Comments of Edwards Lifesciences, LLC
on the National Coverage Analysis
for Transcatheter Aortic Valve Replacement (TAVR)
(CAG-00430N)

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I. Clinical Evidence Demonstrates Effectiveness of Edwards SAPIEN Transcatheter Aortic Heart Valves

A. Aortic Stenosis Disproportionately Impacts Medicare Beneficiaries

Aortic stenosis (AS) is the most common valvular heart condition evaluated, treated and managed by heart specialists in developed countries.[9] After symptom onset, AS rapidly becomes a disabling disease with high mortality and costs. In the United States (US), AS is a major cause of cardiovascular morbidity and mortality in the elderly, estimated as a principle cause in more than 13,000 deaths annually and a contributing factor in many more.[10] The prevalence of AS in individuals 65 years or older is approximately 2% and increases to 4% after the age of 85 years.[11] In a recent study of high-risk Medicare beneficiaries with AS, medically managed patients reported significant end-of-life costs, resulting in annual medical expenditure of approximately $30,000 per patient and average spending 3.4 times higher than the average Medicare beneficiary.[12]

1. Aortic Stenosis is an Insidious Disease

AS is the narrowing of the valve opening that results in decreased blood flow from the left ventricle to the aorta. It is predominantly an age-related disease, resulting from the deposition of calcium on the aortic valve leaflets -- but may also begin as the result of infection, rheumatic fever, or a congenital abnormality. Typically, the valve tissue becomes scarred, inflamed, or thickened, with the collection of calcium reducing the flexibility of the valve leaflets. As it becomes harder to push blood through the valve, the muscles of the heart chamber wall stretch and thicken, leading to an increased likelihood of heart failure.

The natural history of AS in adults consists of a prolonged latent period during which morbidity and mortality are low. Typically, patients with AS are free from cardiovascular symptoms (e.g., angina, syncope, dyspnea, and heart failure) until late in the course of the disease. However, patients with severe AS present with a higher New York Heart Association's (NYHA) Functional Classification score, more pronounced cardiac symptoms (cardiomegaly and congestive heart failure), less exercise tolerance, compromised physical abilities and suffer more often from depression. Survival analyses of this patient group have demonstrated that the interval from onset of symptoms to time of death is, on average, two years in patients with heart failure, three years in those with syncope, and five years in those with angina.[1] Disease progression can be even more insidious in patients with medical conditions and/or cardiovascular abnormalities that result in high or prohibitive surgical risk. In this population, one-year survival in medically managed patients is approximately 55%, ranging from 40% to 70%.[3,12-23]

These high-risk or inoperable patients also suffer from significant degradations in quality of life. Many are classified as either III or IV on the NYHA functional classification scale, meaning they have significant limitations on their ability to undertake physical activity, and often suffer from fatigue, palpitations or dyspnea. Class IV patients suffer from cardiac insufficiency at rest and are unable to undertake any

physical activity without discomfort; many are bedridden.[‡] A recent study of inoperable patients' quality of life found that, on average, their baseline SF-12 physical scores were >2 standard deviations below the United States population norm -- illustrating that their physical well-being is significantly compromised.[5]

2. Valve Replacement is the Only Effective Treatment Option

The treatment of choice for severe symptomatic AS is surgical aortic valve replacement (AVR). In these patients, valve replacement is the only treatment option shown to improve survival and provide durable improvements in related symptoms.[2,24-30] Therefore, in the absence of serious comorbidities, AVR is indicated in virtually all patients.[2] However, advanced age, serious comorbidities, and frailty may render AVR risky or even unfeasible in some patients. Historically, such patients often refused or were denied surgery.[31-33]

Recovery from open surgical AVR involves challenging side effects which are not typically considered adverse events, but which do have a significant impact on providers, patients, and caregivers. Post-operatively, open-heart surgical procedures are associated with prolonged mechanical ventilation, renal complications, pneumonia and other infections, blood loss, and chronic pain. After open-heart surgery, patients have longer recovery times, as they are typically moved to an intensive care unit or discharged to a rehabilitation facility, extending their stay. Consequently, caregivers may experience increased physical and financial burdens.[34-42]

In multiple studies conducted at different hospitals and in different countries, at least 33% of all patients with severe symptomatic AS were medically managed.[32,33,43-49] Medical management consists of pharmacologic treatment to alleviate symptoms and, in certain cases, balloon aortic valvuloplasty (BAV) to enlarge the aortic valve opening. It has not proven possible to achieve sustained symptom relief or to alter the hopeless course of the disease with medical management. Mean survival rates at one, two and three years in high-risk medically managed patients with severe AS are approximately 55%, 35% and 12% respectively.[3,12-23,50]

For these high-risk and inoperable patients with severe symptomatic AS, TAVR has emerged as a successful alternative therapeutic option.

B. TAVR Developed as Alternative for High-Risk and Inoperable Patients

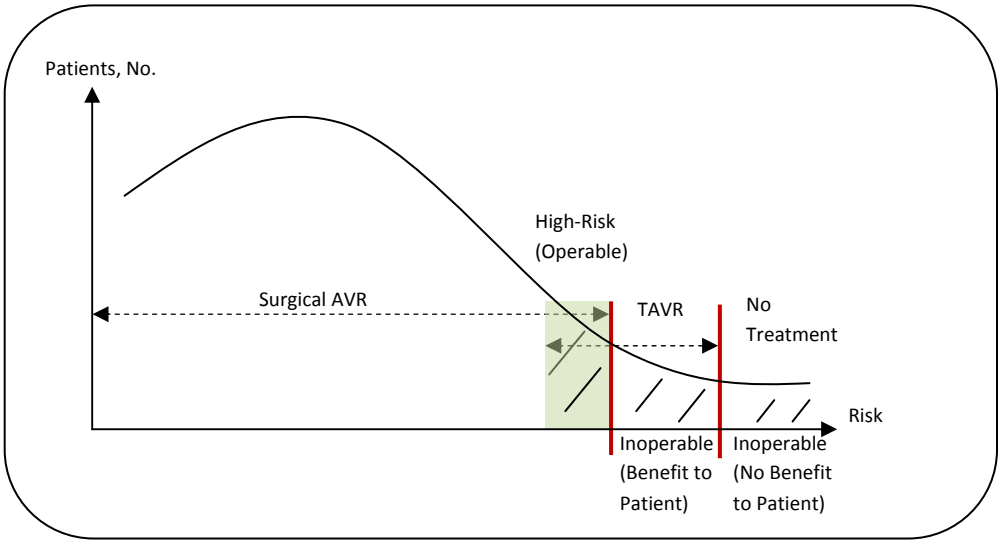
TAVR is a procedure in which the native aortic valve is replaced with a bioprosthetic valve delivered via catheter. Although the native valve is left in situ, it is permanently and invariably destroyed in the placement of the transcatheter heart valve (THV). Two catheter-based approaches are common: the transfemoral (TF) arterial delivery and the direct transapical (TA) approach.

TAVR has been studied in patients considered to be high-risk operative or inoperable. A conceptual map of the severe symptomatic AS treatment continuum is provided in Figure 1. In The PARTNER Trial, high-risk operative patients were defined as those with a Society of Thoracic Surgeons' (STS) predicted risk of

[‡] The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256

mortality ≥ 10%, a Logistic EuroSCORE ≥ 20%, or the presence of comorbidities such that study investigators agreed that the patient's predicted risk of operative mortality was ≥ 15%. Because current surgical risk algorithms, by definition, do not include inoperable patients, the non-operative status of these patients was determined based on a consensus assessment by study investigators. In the PARTNER Trial, inoperable patients presented with comorbidities such that their predicted risk of mortality or serious irreversible morbidity with surgery was ≥ 50% at 30 days.

Figure 1: Conceptual Map of Severe Symptomatic AS Treatment Continuum



While estimating the number of Medicare beneficiaries who might be expected to receive TAVR is difficult, we believe the Requestors'[§] estimate of 5,000 total TAVR procedures per year is low. Estimates of the size of the inoperable and high-risk patient populations vary widely but, in our review, only the most conservative of these would lead to the Requestors' estimated population. We believe annual procedural volume will likely be greater than 5,000. Moreover, the Requestors' belief that only 2/3 of TAVR patients will be Medicare eligible seems misplaced in light of the 81-year-old average age of patients in the TAVR literature.

Providing appropriate and timely access to TAVR is especially important in light of the sick and frail nature of the target population as well as the insidious disease process. In a recent study, 12% of patients referred for TAVR died during the work-up process between screening and final treatment,[51] clearly underscoring the need for ready access to screening and rapid availability of this therapy.

[§] In this document, Requestors refers to The Society of Thoracic Surgeons and The American College of Cardiology

C. TAVR's Evidence Base is Robust

Since the first transcatheter aortic valve was delivered in 2002 by Dr. Alain Cribier,[52] Edwards transcatheter heart valves have been implanted in more than 25,000 patients in 51 countries worldwide. This global experience has translated into a robust body of evidence documenting procedural outcomes. This evidence base includes the largest randomized TAVR clinical trial, the Placement of Aortic Transcatheter Valves, or The PARTNER Trial, and a number of single-center and multicenter trials, with currently published peer-reviewed manuscripts representing thousands of patients in both pre- and post-commercialization settings. The available evidence demonstrates the positive impact of TAVR on survival,[3,53-59] hemodynamic performance,[3,53,56,57,60-93] clinical outcomes at or beyond 3 years,[67,72,94] NYHA functional class,[3,53] quality of life,[5,95-100] cost-effectiveness[8] and the generalizability of outcomes (see section I.E.).

1. The PARTNER Trial – A Landmark Randomized Clinical Trial

The PARTNER Trial (NCT00530894), initiated in 2007, was the first randomized clinical study to investigate the safety and effectiveness of TAVR. More than 1,000 severe symptomatic AS patients were assigned to one of two independently powered arms: a "non-surgical" arm (Cohort B), in which patients who were determined to be inoperable were randomized to either treatment with the Edwards SAPIEN THV (delivered transfemorally) or standard therapy, and a "surgical" arm (Cohort A), in which high-risk operable patients were randomized to either treatment with the Edwards SAPIEN THV (delivered transfemorally or transapically) or surgical AVR. The primary endpoint was all-cause mortality at one year. Patients will be followed for five years.

The PARTNER Trial met its predetermined clinical endpoints and demonstrated that TAVR offers significant survival benefits over standard therapy for inoperable patients, and is an equivalent therapeutic alternative to the gold-standard therapy of surgical AVR in high-risk patients. Equally compelling quality-of-life and cost-effectiveness studies were conducted alongside the clinical study. Details on each Cohort of The PARTNER Trial, as well as the related studies, are provided in the *Overview of Key Studies* section below.

The PARTNER Trial required a paradigm shift on behalf of the clinicians involved, as it required a "heart team" approach to provide optimal treatment for each patient. The trial was characterized by extensive training and rigourous study management, and was structured around an interdisciplinary approach focused on the interventional cardiologist and the cardiothoracic surgeon. Patients were carefully screened for inclusion using established surgical risk algorithms and advanced imaging, including the use of computed tomography to assess the suitability of the access vessels.

Results of The PARTNER Trial were adjudicated by an independent data and safety monitoring board, a clinical events committee, an echo core laboratory, and an independent biostatistical core laboratory, as appropriate.

2. *Supplemental Literature Supports the Findings of The PARTNER Trial*

In addition to The PARTNER Trial, there is a vast body of other evidence related to TAVR and relevant treatment alternatives, as demonstrated by a systematic review of peer-reviewed scientific literature, supplemented with clinical presentations from medical conferences. For our systematic review, publications were required to meet the criteria listed in *Table 1* below to be eligible for inclusion. Additional, intervention-specific criteria were also applied.[**] For a detailed description of the search strategy and results, see *Appendix A*.

Table 1: Inclusion and exclusion criteria for publications on TAVR and relevant treatment alternatives

Characteristic	Criteria
Publication type	Peer-reviewed publications reporting clinical outcomes. Reviews, editorials, letters, and animal studies excluded.
Population	Elderly patients (mean study age ≥ 70 years) with severe AS considered inoperable or at high surgical risk
Interventions	TAVR, medical management with or without BAV, and AVR. For TAVR studies, trials must include patients receiving Edwards transcatheter aortic heart valves. Mixed populations of Edwards and non-Edwards (i.e., CoreValve) THVs included. Exclusively non-Edwards THVs excluded.[††]
Clinical outcomes	Survival data including (at least) 30-day outcomes. In-hospital survival may be used as a proxy in the absence of 30-day results
Study characteristics	Clinical studies, excluding case reports, ≥ 15 patients
Language	English
Time period	Medical management and AVR publications were excluded if dated before 1989. TAVR studies were excluded if dated before 2005 to best reflect contemporary transcatheter heart valves, delivery systems and procedural approaches

The TAVR clinical overview is composed of 55 peer-reviewed published manuscripts from four feasibility trials,[68-71] one randomized study (with two cohorts),[3,53] one European post-marketing study,[54,55] one compassionate clinical use trial,[56] five national registries,[59,66,73,101,102] and 41 single and multicenter observational studies.[57,60-65,67,72,74-94,103-113]

Across all studies, mean patient age was 81 years, STS Score was 12% and Logistic EuroSCORE was 28%. Procedural success was achieved in 96% of patients and 30-day mortality was 9%. One, two, and three year survival was 76%, 69%, and 59%, respectively. Importantly, no structural valve deterioration has been reported even at five years among the earliest recipients of the therapy.[114] Among studies reporting hemodynamic performance, significant improvements in aortic valve area and mean and peak gradients have been consistently observed after TAVR.[3,53,56,57,60-93] Serious adverse events potentially

[**] Early TAVR feasibility (first-in-man) studies using an antegrade trans-septal approach are excluded because this approach was abandoned and replaced by a retrograde approach due to its procedural complexity. AVR studies were eligible for inclusion if the patients met the following criteria: Logistic EuroSCORE threshold ≥ 20% or mean Logistic EuroSCORE ≥ 25%, STS ≥ 10, or predicted mortality ≥ 15% using other validated risk-scoring systems (i.e., Ambler).

[††] Because the pending National Coverage Determination is expected to be finalized in 2012 when only the SAPIEN THV is anticipated to be available, this evidence review focuses on studies documenting clinical outcomes in Edwards THVs. The introduction of alternative THVs (such as CoreValve) are not anticipated until 2014 or beyond and thus, studies exclusively describing non-Edwards THVs were excluded.

associated with the procedure include: stroke or transient ischemic attack (TIA), major vascular complications, renal failure, pacemaker implantation, conversion to AVR, bleeding, paravalvular leak, myocardial infarction, valve embolization, and new atrial fibrillation (*Appendix C*).

D. Overview of Key Studies

1. Feasibility Studies

Between 2005 and 2007, four TAVR feasibility studies were initiated by Edwards in the United States (Revival II) and in Europe (Revive II, TRAVERCE and PARTNER EU) in over 500 patients. Details on these studies, the number of patients enrolled, and survival at one, six, and twelve months can be found in *Appendix B, Table 9*. Despite reflecting very early clinical experience, these studies demonstrated consistent valve performance and established feasibility for the TAVR approach, leading to the initiation of the pivotal US Investigational Device Exemption (IDE) clinical trial.

2. The PARTNER Trial

The PARTNER Trial was a prospective, randomized, controlled, multicenter trial evaluating the safety and effectiveness of the Edwards SAPIEN THV. The trial included two individually stratified and powered cohorts with severe symptomatic AS patients who were assessed to be inoperable (Cohort B) or operable but at high surgical risk (Cohort A). Patient screening and assessment of operable status was conducted by a multi-disciplinary steering committee that included both cardiac surgeons and interventional cardiologists. Once a patient was assigned to a Cohort and randomized, decisions about the care of each individual patient, including the ultimate decision to proceed with the assigned treatment, were left to the co-investigator teams of cardiac surgeons and interventional cardiologists at the site.

a) Cohort B

The results of Cohort B of The PARTNER Trial were published by the New England Journal of Medicine in September 2010 and are summarized below.[3] Inoperable patients were randomly assigned to either TAVR (transfemoral) or best medical management including frequent use of BAV (standard therapy). The co-primary endpoints were all-cause mortality for the duration of the trial (superiority) and a composite of all-cause mortality and recurrent hospitalization (superiority). Treatment groups were generally well balanced at baseline (TAVR mean age 83 years, Log ES 26%, STS 11%; standard therapy mean age 83 years Log ES 30%, STS 12%). 30-day mortality did not differ statistically between groups (5% vs. 2.8%, for TAVR and standard therapy, respectively, p=0.41). However, at one year, TAVR showed a significant reduction in all-cause mortality (30.7% vs. 50.7% for TAVR and standard therapy, p<0.001). Also significantly reduced were cardiovascular mortality (19.6% vs. 41.9% for TAVR and standard therapy, p<0.001), all-cause mortality or major stroke (33% vs. 50.3% for TAVR and standard therapy, p<0.001) and all-cause mortality or repeat hospitalization (42.5% vs. 70.4% for TAVR and standard therapy, p<0.001).

Not surprisingly, TAVR was superior to standard therapy in valve performance, with echocardiographic findings at 30 days showing:

- Increased valve area from 0.6 to 1.5 cm^2, p<0.001
- Decreased valve gradient from 45 to 11.1 mmHg, p<0.001

In this population and in the setting of early operator experience and first generation delivery systems, TAVR resulted in more frequent complications at 30 days vs. standard medical therapy, including:

- Major vascular complications, 16.2% vs. 1.1%, p<0.0001
- Major bleeding episodes, 16.8% vs. 3.9%, p<0.0001
- All stroke or TIA, 6.7% vs. 1.7%, p=0.03
- Major strokes, 5.0% vs. 1.1, p=0.06

Standard therapy did not alter the dismal natural history of severe symptomatic AS. The number of patients needed to treat to save a life in this trial was only five. Based on these findings, the authors concluded that the benefits outweigh the risks associated with balloon-expandable TAVR when used in the studied indication, and, in the New England Journal of Medicine, stated in September 2010 that TAVR should be considered the "new standard of care" for this patient population.[3] For more details, see *Appendix B, Tables 10-11 and Appendix C.*

Two-year survival results from Cohort B will be reported in November 2011, at the Transcatheter Cardiovascular Therapeutics conference (TCT) in San Francisco.

b) Cohort A

The results of Cohort A were published by the New England Journal of Medicine in June 2011 and are summarized below.[7,53] Patients assigned to Cohort A were first assessed for suitable transfemoral access. TF was the preferred placement method, with TA reserved for those with poor ilio-femoral vasculature characteristics. Those assigned to the TF placement group were randomized to either a TAVR (TF) or AVR treatment arm. In the absence of suitable peripheral anatomy, patients were assigned to a TA placement group, and similarly randomized between TAVR (TA) or AVR. The primary endpoint was all-cause mortality at one year (non-inferiority). The groups were generally well balanced at baseline with similar age and risk profiles (TAVR mean age 84 years, Log ES 29%, STS 12%; AVR mean age 85 years, Log ES 29%, STS 12%). Given the technical differences in the TA and TF approaches, and the resulting differences in procedural outcomes, data for each arm are presented separately below. Similarly, for completeness, we've included a summary of both the intention-to-treat (ITT) and the as-treated (AT) analyses. The as-treated analysis has increased significance in light of the fact that 42 of the 699 randomized patients refused or failed to receive the treatment to which they were assigned. The great majority (90%) of these patients were in the AVR arm, potentially underscoring the challenges associated with open-heart surgery in high-risk and elderly patients.

(1) Transfemoral Approach

In the intention-to-treat analysis, 30-day mortality was 3.3% and 6.2% for TF and AVR, respectively (p=0.07), and one year survival was 77.8% and 73.6% for TF and AVR, respectively (p=0.29). On this basis, the TF cohort was non-inferior to AVR (p=0.002). In the as-treated analysis, 30-day mortality was

3.7% and 8.2% for TF and AVR, respectively (p=0.046), and one year survival was 78.7% and 74.8% for TF and AVR, respectively (p=0.33).

Important but different peri-procedural hazards exist for both transfemoral TAVR and AVR. Adverse neurological events were more common in TF patients – with higher rates of all stroke or TIA (4.6% vs. 1.4% - AT, p=0.04); however, differences in major stroke rates (2.5% vs. 1.4% - AT, p=0.37) were not statistically significant. All and major vascular complications also occurred more frequently in the TF group (23% vs. 3.6% and 14.2% vs. 3.2%, respectively p<0.001). By contrast, major bleeding (23.1% vs. 10.9%, p<0.001) and new atrial fibrillation (18.6% vs. 7.45%, p=0.001) were more frequent in AVR patients as compared to TF. More details on transfemoral peri-procedural hazards can be found in *Table 2* below.

Table 2: Key transfemoral peri-procedural hazards (30-day)

Outcome	Intention to treat			As treated		
	TF	AVR	p value	TF	AVR	p value
All stroke or TIA	5%	1.7%	0.04	4.6%	1.4%	0.04
Major stroke	2.9%	1.7%	0.37	2.5%	1.4%	0.37
All vascular complications	22.7%	3.3%	<0.001	23%	3.6%	<0.001
Major vascular complications	14.0%	2.9%	<0.001	14.2%	3.2%	<0.001
Major bleeding	9.5%	20.2%	<0.001	10.9%	23.1%	<0.001
New Afib	7.4%	16.5%	0.006	7.45%	18.6%	0.001

(2) Transapical Approach

In the intention-to-treat analysis, 30-day mortality was 3.8% and 7.0% for TA and AVR, respectively (p=0.32), and one year survival was 71% and 72.1% for TA and AVR, respectively (p=0.85). While not powered for independent statistical analysis, the TA cohort showed similar results as AVR. In the as-treated analysis, 30-day mortality was 8.7% and 7.6% for TA and AVR, respectively (p=0.79), and one year survival was 70.9% and 74.7% for TA and AVR, respectively (p=0.55). The peri-procedural hazards are highlighted in the table below. Adverse neurological events trended higher in the TA group; however, as expected, all and major vascular complications were comparable between treatment arms and major bleeding occurred more frequently in the AVR group. More details on the transapical peri-procedural hazards can be found in *Table 3* below.

Table 3: Key transapical peri-procedural hazards (30-day)

Outcome	Intention to treat			As treated		
	TA	AVR	p value	TA	AVR	p value
All stroke or TIA	6.8%	4.2%	0.43	7.9%	5.5%	0.50
Major stroke	5.8%	3.2%	0.37	7.0%	4.4%	0.45
All vascular complications	3.8%	4.9%	0.70	4.8%	5.4%	0.85
Major vascular complications	3.8%	3.9%	0.97	3.9%	4.3%	0.87
Major bleeding	8.7%	17.9%	0.05	8.8%	21.8%	0.01
New Afib	11.5%	14.6%	0.54	11.5%	16.3%	0.41

(3) Overall Cohort A Results

In the overall cohort, 30-day mortality was lower in the TAVR group as compared to AVR (3.4% vs 6.5%, p = 0.07), though not statistically significant. At one year, survival was comparable between groups: mortality was 24.2% and 26.8% for TAVR and AVR, respectively, p=0.001 for non-inferiority.

Both TAVR and AVR provided consistent valve performance with slightly superior results at one year in the TAVR group with respect to:

- Mean aortic-valve gradient (10.2 vs. 11.5 mmHg, p=0.008)
- Aortic-valve area (1.59 vs. 1.44 cm^2, p=0.002)

Moderate or severe paravalvular regurgitation was more common in the TAVR group at 30 days (12.2% vs. 0.9%) p<0.001 and 1 year (6.8% vs. 1.9%), p<0.001.

In the combined analysis, both TAVR and AVR were associated with important but different peri-procedural hazards. The occurrence of major bleeding events (19.5% vs. 9.3%, p<0.001) and new onset atrial fibrillation (16% vs. 8.6%, p=0.006) were higher in the AVR group, while TAVR resulted in more frequent adverse neurological events (all strokes and TIAs 5.5% vs. 2.4%, p=0.04) and major vascular complications (11.0% vs. 3.2%, p<0.001).

Of note, the study also found that compared to AVR, there were reductions in hospital length of stay (8 vs. 12 days, p<0.001), ICU length of stay (3 vs. 5 days, p<0.001), total procedure time (133 vs. 230 min) and anesthesia time (236 vs. 330 min) for TAVR procedures.[6,53]

At 30-days, symptom improvement favored TAVR with more patients in the transcatheter group experiencing a reduction in cardiac symptoms to NYHA class II or lower (p<0.001). Similarly, among patients who could perform six-minute walk tests at 30-days, TAVR patients walked farther (median distance [m] 128 vs. 75 for TAVR and AVR, respectively; p=0.002). At one-year, both treatment groups noted improvement in cardiac symptoms and functional capacity, with no significant between group differences.

In summary, both TAVR approaches (TF or TA) and AVR are acceptable therapies in high-risk patients, with important but different peri-procedural hazards and post-operative requirements that are likely to impact case-based decision making. Based on these findings, The PARTNER Trial investigators concluded that "in the absence of long-term follow-up data, recommendations to individual patients must balance the appeal of avoiding the known risks of open-heart surgery against the less invasive transcatheter approach, which has different and less well understood risks, particularly with respect to stroke."[53] For more details, see *Appendix B, Tables 10-11* and *Appendix C*.

3. Registries and Observational Research

a) The SOURCE Registry

The SOURCE Registry is the largest collection of real-world post-market outcomes in patients receiving the Edwards SAPIEN THV. Cohort 1 of the registry included all 1,038 (TF = 463; TA = 575) consecutively enrolled patients from 32 European centers between November 2007 and January 2009.[55] Patient selection for TAVR was based on multidisciplinary team assessment, and all patients were considered high-risk for surgery or inoperable. Generally, patients had a Log ES > 20% (mean of 25.7% and 29.1% for TF and TA, respectively) and age >80 years. At baseline, the two patient populations differed in several ways – the TA cohort presented with:

- A higher predicted risk of mortality
- More renal dysfunction
- A higher incidence of coronary artery disease, porcelain aorta, prior CABG and mitral valve disease

Procedural success was 93.8% and 30-day mortality was 6.3% for transfemoral procedures and 10.3% for the transapical approach.[55] Overall survival at one year was 76%.[54]

An extension (Cohort 2) of The SOURCE Registry was performed between February and December 2009 with the inclusion of an additional 1,269 patients (TF = 457; TA = 812). One-year outcomes of the pooled Cohort 1 and 2 analysis were presented in May 2011 at the European Association of Percutaneous Cardiovascular Interventions official congress (EuroPCR). Based on the Kaplan-Meier analysis, overall one and two-year survival were 76.5% and 67.7%, respectively.[115] For more details, *see Appendix B*, *Table 14*.

b) Canadian Compassionate Use Study

The Canadian Edwards TAVR Multicenter Experience study included 339 (TF=167; TA=172) consecutively enrolled patients at the six centers participating in the Canadian Compassionate Clinical Use program. Enrollment took place between 2005 and 2009; Edwards' valves (Cribier-Edwards, SAPIEN, or SAPIEN XT) were used in all cases. Similar to The SOURCE Registry, patient eligibility was based on high surgical risk or inoperability, and the TA cohort had a statistically higher surgical risk than the TF group (STS 10.5% and 9.0%, respectively) at baseline. For the overall study population, procedural success was 93.3%, and 30-day mortality was 10.4%. Survival rates at one and two years were 76% and 64%, respectively.[56]

c) National TAVR registries

Since the commercial introduction of TAVR in Europe in 2007, France, Germany, Belgium, Italy and the United Kingdom (UK) have published results from national registries. The registries include consecutively enrolled TAVR patients with both the SAPIEN and CoreValve transcatheter valves and the TF and TA approaches. High procedural success was consistent across all registries (97-99%).[59,66,73,101,102] Thirty-day mortality and stroke ranged from 7% to 13% and 3% to 5%, respectively.[59,66,73,101,102] One-year survival rates were reported in the Belgian, Italian and UK registries (76%, 81% and 79%, respectively); and two-year survival was 72% and 74% in the Italian and UK registries, respectively.[59,101,102] For more details, see *Appendix C.*

d) Other TAVR Observational Studies

In addition to the aforementioned literature, there are at least 41 other peer-reviewed, published studies that document clinical outcomes in TAVR recipients. The mean 30-day survival across all 41 studies was 91%. Mean survival at one year was 78%, ranging from 64% to 85%, and survival rates at two and three years were 69% and 59%, respectively. For more details, see *Appendix B, Table 15.*

E. Evidence is Generalizable to Medicare Population

When evaluating the ability to generalize TAVR evidence to the Medicare population, there are three primary considerations. First, does the evidence demonstrate consistent clinical outcomes across patient experience relative to alternative treatments; second, does the evidence demonstrate that results are obtainable outside the investigational setting; and third, is the population studied representative of the Medicare population.

1. <u>Consistent Clinical Outcomes</u>

The 55 TAVR studies reviewed demonstrate consistency of outcomes across patients. Clinical benefit relative to treatment alternatives is evident in The PARTNER Trial and in the body of evidence for severe AS patients at high or prohibitive surgical risk. Among inoperable patients, the only alternative to TAVR is medical management. The literature review identified 14 studies that were useful in describing survival in high-risk operable and inoperable patients with severe AS receiving medical management (± BAV). One additional study was identified from a medical conference. The results underscore the dismal prognosis in this elderly and frail patient population if the severely diseased heart valve is not replaced. The mean survival rates at one, two, and three years were 55%, 35%, and 12%, respectively (*Appendix B, Table 16*). These finding corroborate the poor prognosis of medically managed patients (50% survival at one year) in Cohort B of The PARTNER Trial and confirm that TAVR offers a significant survival benefit (70% survival at one year) in this patient population.

Among high-risk operable patients, the alternative to TAVR is surgical AVR. In order to make a valid comparison to TAVR it is important to carefully select studies with similar high-risk patients. To date, there has been little overlap outside The PARTNER Trial (Cohort A) between the patients who have received surgical AVR and those who have received TAVR.[116] Despite the inherent limitations of observational research, the literature review identified 12 studies that were useful in documenting survival in high-risk patients undergoing surgical AVR. One additional study was identified from a

medical conference. Across these studies, mean survival rates in this high-risk AVR group at 30 days, one year, two years, and three years were 89%, 76%, 66%, and 58%, respectively (*Appendix B, Table 17*). By comparison, the mean survival rates in the TAVR literature (high-risk operable and inoperable) at 30 days, one year, two years, and three years were 91%, 76%, 69%, and 59%, respectively (*Appendix C, Table 18)*. These survival rates suggest the transcatheter approach is comparable to AVR in selected high-risk patients.

Table 4: Summary of key survival endpoints for TAVR and relevant treatment alternatives

Source	Treatment	Patient Population	Survival 30 day	1 year	2 year	3 year
The PARTNER Trial Cohort B	TAVR	Inoperable	95%	69%	--	--
	Med Rx (standard therapy)	Inoperable	97%	49%	--	--
The PARTNER Trial Cohort A	TAVR	High-risk	97%	76%	--	--
	AVR	High-risk	93%	73%	--	--
Literature Review	TAVR[‡‡]	High-risk & inoperable	91%	76%	69%	59%
	AVR[§§]	High-risk	89%	76%	66%	58%
	Med Rx[***]	High-risk & inoperable	91%	55%	35%	12%

Appendix C provides a detailed summary of all TAVR studies from the literature search.

2. Experience Outside the Investigational Setting

In Europe, where initial post-commercialization data has been reported on and published through use of the SOURCE Registry, TAVR 30-day mortality rates remained as good or better after the procedure had been adopted outside of the initial investigational sites. For example, the 30-day survival rates in early investigational transfemoral studies ranged from 92-93%,[55,56] while SOURCE data reported a comparable survival rate of 93.7% for the initial year post-commercialization. Similarly, early investigational 30-day survival rates for transapical studies ranged from 81-85%.[69-71] By comparison, 30-day survival data from The SOURCE Registry reported average transapical survival rates of 89.7% in the initial year post-commercialization.[55] Moreover, two-year data from the SOURCE registry (Cohorts 1 & 2) reported average 30-day survival rates for transfemoral and transapical cases of 92.5% and 89.1%, respectively, indicating that outcomes remained relatively consistent in new centers not part of the early investigational studies.[115]

With respect to the US clinical data, the Requestors cite a higher mortality rate from European post-market registry data as compared to the intention-to-treat PARTNER Trial[6] results. We note that this comparison is inappropriate, due to the different procedural and patient characteristics in these groups. For instance, The SOURCE Registry[117,118] includes a significantly higher percentage of transapical procedures – an approach generally associated with higher mortality rates – than The PARTNER Trial (55% vs. 19%). The SOURCE Registry also uses different patient inclusion and exclusion criteria.

[‡‡] Survival estimates based on calculated mean from 55 peer-reviewed published TAVR articles; see *Appendix C*
[§§] Survival estimates based on calculated mean from 13 studies; see *Appendix B, Table 15*
[***] Survival estimates based on calculated mean from 15 studies; see *Appendix B, Table 14*

A comparison of approach-specific outcomes in patients who actually received TAVR (as-treated) reveals that the PARTNER Trial results are, in fact, broadly comparable to those of the SOURCE Registry. Among transfemoral patients in Cohorts A (high-risk operable) and B (inoperable) of The PARTNER Trial, 30-day mortality rates were 3.7% and 6.4%, respectively.[3,7,53] In the SOURCE Registry, which includes both high risk and inoperable patients, transfemoral 30-day mortality rates were 6.3%.[55] Similarly, among transapical patients in Cohort A of the PARTNER Trial, 30-day mortality rates were 8.7% (as-treated analysis) compared to 10.3% in the SOURCE Registry.[7,53,55]

One-year survival was also comparable on an as-treated basis. For instance, among transfemoral patients in Cohort A of The PARTNER Trial[†††], one-year mortality was 21.3% compared to 18.9% in the SOURCE Registry. Similarly, among transapical patients in Cohort A, one-year mortality was 29.1% compared to 27.9% in the SOURCE Registry.[7,53,54] Thus, upon closer scrutiny, The PARTNER Trial results are not inconsistent with the commercial experience in Europe as reflected in the SOURCE Registry, and both European and US investigational studies appear to be generalizable.

3. Population Studied is Comparable to Medicare

AS is predominately an age-related condition affecting approximately 2% of individuals 65 years or older, increasing to 4% after the age of 85 years.[11] The mean age of TAVR patients reported in the 55 studies reviewed previously was 81 years. In a recent five-year outcomes study of the Medicare population with severe AS, the mean age of high-risk patients treated with medical management and AVR was 85 and 78 years, respectively. The mean Logistic EuroSCORE was 34% and 37% for high-risk patients with medical management and AVR, respectively. Survival at one, two, three, four and five years was 42%, 25%, 15%, 9%, and 5%, respectively, for medically managed patients and 60%, 55%, 47%, 40%, and 34%, respectively, for AVR patients.[12,119]

[†††] One-year mortality rates on an as-treated basis were not provided in Cohort B

II. Quality of Life Evidence Demonstrates Significant Improvements in TAVR patients

While morbidity and mortality outcomes are crucial, so too are the emotional, physical, functional and mental effects of a therapy, particularly in an elderly population.[98] In fact, for patients with severe heart failure and the elderly in general, improvements in symptoms, functional status and quality of life (QOL) may be even more important than improvements in longevity.[5,120]

To date, the best available evidence on QOL in TAVR patients comes from The PARTNER Trial. The QOL results from Cohort B (inoperable patients) were published in the journal Circulation in October 2011 and are summarized below.[5] Three separate instruments were used in the trial to collect QOL data, as outlined in *Table 5* below. Clinically relevant and statistically significant changes in QOL were observed as early as one month post-procedure with a 13.3-point improvement ($p< 0.001$) in overall Kansas City Cardiomyopathy Questionairre (KCCQ) summary scores compared with the standard therapy group. Even larger clinically relevant changes in QOL were observable in the TAVR group at six months (mean difference 20.8 points, $p<0.001$) and 12 months (mean difference 26 points, $p< 0.001$). At one year, these benefits approximate a two-level improvement in NYHA functional class.[5] In the KCCQ subscales, large clinically relevant differences were observed in the Symptom, Physical, QOL and Social Limitations scores. It is important to note that every subgroup of the TAVR treatment group had a large, clinically relevant and superior QOL benefit. Additionally, when QOL was considered with survival, the number needed to treat to obtain an excellent outcome (i.e., one-year survival with ≥ 20-point improvement in KCCQ) was approximately 3.5. The other generic utility instruments showed equally significant improvements for TAVR patients. Gains in the SF-12 physical component were equivalent to a ten-year reduction in effective age.[5,121]

Table 5: QOL instruments used in The PARTNER Trial

Instrument	Description/Role
Kansas City Cardiomyopathy Questionnaire (KCCQ)	Heart failure-specific Domains: symptoms, QOL, self-efficacy, physical limitation, social limitation Scores: 0-100 (higher = better)‡‡‡
SF-12	General physical and mental health Scores standardized such that mean = 50, standard deviation = 10 (higher = better)
EQ-5D (EuroQOL)	Generic instrument for assessment of utilities and QALYs Scores 0-1 (0 = death: 1 = perfect health)

Based on the findings, the authors conclude that despite multiple comorbid conditions and advanced age, patients similar to those enrolled in this trial can expect very meaningful improvements in symptoms, functional status, and quality of life after TAVR.[5]

A similar analysis of the quality of life implications of TAVR for high-risk surgical patients enrolled in Cohort A of The PARTNER Trial has been conducted by Matthew R. Reynolds, et. al., and has been

‡‡‡ The KCCQ uses the following scale for interpretation: A change in score of 5 points is considered a small but clinically important change, a change in score of 10 points is considered a moderate clinically important change, and a change in score of 20 points is considered a large clinically important change.

accepted for presentation at the Transcatheter Cardiovascular Therapeutics conference in November 2011.

Importantly, several smaller prospective studies of high-risk and inoperable patients have also documented improvements in health status after TAVR; however, none of these studies included a parallel control group. Table 6 provides a summary of findings from the selected studies measuring the impact of TAVR on QOL.

Table 6: Summary of findings from selected QOL studies

Reference	Characteristics	N	Instrument	Primary Findings
Goncalves et al. 2011[122]	Age 82, Log ES 19%	74	Minnesota Living with Heart Failure Questionnaire (MLHFQ)	Global, physical and emotional MLHFQ scores significantly improved 6.5 months after TAVR. All patients showed a clinically meaningful change in total score.
Krane et al. 2010[99]	Age 81, Log ES 20%	99	Short Form 36 Health Survey Questionnaire (SF-36)	The scores for physical functioning, bodily pain, general health and vitality were significantly improved 3 months after TAVR. No significant changes were found for role-physical, social functioning and mental health. The score for role-emotional decreased 3 months after TAVR compared with the preoperative score.
Lefevre et al. 2010[69]	Age 82, Log ES 30%, STS 12%	130	Kansas City Cardiomyopathy Questionnaire (KCCQ) EQ-5D (EuroQOL)	EQ-5D demonstrated marginal improvement at 1 year post-TAVR. The KCCQ overall summary score demonstrated a significant improvement from baseline to 1 year.
Reynolds et al. 2008[123]	Age 83, "inoperable"	75	Short Form-12 (SF-12) Kansas City Cardiomyopathy Questionnaire (KCCQ)	At baseline, physical health and cardiac-specific QOL were markedly impaired. At 6 months, significant improvements were seen in both the SF-12 and KCCQ scores.
Svensson et al. 2008[70]	Age 83, STS 13%	40	Short Form-12 (SF-12)	Scores improved for both physical functioning and mental health at 6 months post-TAVR, with the physical improvements considered significant.

III. Economic Evidence Demonstrates TAVR is Cost Effective

A. US Cost-Effectiveness Analysis Conducted Alongside The PARTNER Trial

A cost-effectiveness analysis was performed in conjunction with The PARTNER Trial, by Matthew R. Reynolds of the Harvard Clinical Research Institute and David J. Cohen of the Mid-American Heart Institute. The initial results were presented in April 2011 at the American College of Cardiology (ACC) Scientific Sessions.[8] The objective of the Cohort B analysis was to understand the incremental costs and cost-effectiveness of TAVR compared with medical management (standard therapy) among inoperable patients with severe AS.[8] Data on survival, QOL, healthcare resource utilization and hospital charges were collected during the trial and used to estimate the incremental cost-effectiveness of TAVR to the US healthcare system. Survival analyses were performed with data collected through at least 12 months of follow-up (mean follow-up duration of 18 months and maximum of 30 months). To estimate life expectancy beyond the trial period, parametric survival models were used to extrapolate survival probabilities.

Mean TAVR admission costs excluding physician fees were $73,563 (median $62,934) and the mean costs including physician fees, were $78,542 (median $67,551). Over the first 12 months of follow-up, hospital care costs were higher in the standard therapy group by $26,025 per patient compared to the TAVR group ($p<0.001$). Including the initial TAVR admission, the total 12-month medical care costs were approximately $52,000 per patient higher in the TAVR group as compared with the standard therapy group ($p<0.001$). Lifetime medical care costs beyond one year were approximately $43,664 per patient for the TAVR group and $16,282 per patient for the standard therapy. These results were largely attributable to the low survival in medically managed patients. Based on the survival models, total life expectancy for the TAVR group was estimated to be 3.1 years, compared with 1.2 years for the standard therapy group– a difference of 1.9 years (1.6 years after discounting).

The incremental cost effectiveness ratio (ICER) for TAVR compared with standard therapy was estimated at $50,200 per life year gained or approximately $62,000 per quality-adjusted life year (QALY) gained. The authors noted this is well within the range of other commonly used technologies in the US. Thus, among inoperable patients with severe AS, TAVR provides a substantial survival benefit at a reasonable incremental cost.

A similar cost-effectiveness analysis of TAVR in high-risk surgical patients enrolled in Cohort A of The PARTNER Trial has been conducted by David J. Cohen, et. al., and has been accepted for presentation at the Transcatheter Cardiovascular Therapeutics conference in November 2011.

B. UK Cost-Effectiveness Analysis

A second cost-effectiveness analysis using clinical data from The PARTNER Trial was conducted by Michael Drummond et.al., to evaluate the TAVR's cost-effectiveness from the perspective of the UK National Health Services. TAVR was found to be cost effective in the inoperable patient population with severe AS. The base-case ICER is £26,100 and remains below £30,000 under all sensitivity analysis scenarios. This analysis has been accepted for presentation at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Europe in November 2011.

IV. Key Coverage Parameters and the Requestors' Recommended NCD

We have reviewed in detail and discussed with the Requestors the evidence supporting coverage and their recommended NCD language. With several modifications described below, we believe the evidence supports the Requestors' language.

In particular, we support the recommended use of dedicated, multidisciplinary heart teams to appropriately select and manage all TAVR patients, and the recommended provision of coverage for both inoperable and high-risk operable patients. To facilitate the heart-team concept, and support patient-centric treatment strategies, it is also essential that any NCD provide coverage for both the transfemoral and transapical approaches. We also agree that to ensure the best possible outcomes, TAVR should be provided in appropriately equipped hospitals, and patient selection for TAVR should conducted by a dedicated heart team, led by cardiac surgeons and interventional cardiologists. This process must also rely on pre-screening imaging to assess vasculature suitability for the possible use of a transfemoral approach, and ongoing consultation among the team to ensure that each individual patient's unique co-morbidities, anatomical characteristics and specific operative risk are considered before the team agrees on the best possible treatment approach.

A. Covered Patient Populations

Patient selection criteria are clearly defined by existing clinical evidence and clinical practice standards. Appropriate patient selection criteria for patients suffering from severe symptomatic aortic stenosis are supported by strong one-year outcomes from The PARTNER Trial, as well as longer term data reported via registry and other multi-center peer-reviewed publications. These data, and the corresponding patient selection protocols, provide the framework for the Requestors' proposal and the basis for an appropriate Medicare TAVR coverage policy. There are two appropriate patient populations for coverage at this time: (1) inoperable patients and (2) high-risk operable patients.

1. Inoperable patients

In the Requestors' proposal, patients are deemed inoperable based on a consensus determination by a multidisciplinary heart team that the predicted risk of mortality or serious irreversible morbidity associated with surgery would outweigh the potential benefit.

In The PARTNER Trial[3] clearly positive outcomes were achieved for inoperable patients selected for TAVR versus standard therapy. Among inoperable patients, one-year mortality from any cause was 30.7% for the TAVR group versus 50.7% for those treated with standard therapy ($p<0.001$). The composite end point of death from any cause or repeat hospitalization was 42.5% with TAVR versus 71.6% for standard therapy ($p<0.001$). NYHA class III or IV cardiac symptoms were lower among TAVR patients than standard therapy patients at one year (25.2% vs. 58.0%, $p<0.001$). Although the increase in major strokes during the 30-day observation period (5.0% in TAVR vs. 1.1% in standard therapy) is notable, patients and providers must weigh this 3.9% increased risk against the reported 20% absolute increase in one-year survival. Notably, the FDA's Circulatory Systems Device Advisory Panel, in July 2011, agreed on a 9-0 vote (with 1 abstention) that the benefits of the SAPIEN THV outweigh the risks for inoperable patients.

Reported survival improvements of this order are uncommon, and were significant enough to prompt the authors of the study to state in the New England Journal of Medicine that TAVR should be the "new standard of care" for these patients.[3]

As importantly for the Medicare population, these improvements in survival where accompanied by very significant observed improvements in patient quality of life -- gains approximating a two-level improvement in NYHA functional class using KCCQ scores. Equally impressive gains on the SF-12 physical component, equivalent to a ten-year reduction in effective age, were also observed. These QOL results underscore the significant and immediate benefits that TAVR offers these patients. And as mentioned above, TAVR has proven to be a cost-effective therapy in this patient population.

2. High-risk operable patients

In the Requestors' proposal, high-risk patients with severe symptomatic AS are defined as those with an STS Risk Score ≥ 8% or the presence of comorbidities such that the cardiac surgeon and cardiologist agree that the predicted risk of operative mortality is ≥ 15%.

The STS risk score is a helpful assessment tool as it relates to TAVR within this cohort. However, several clinical factors of significance to operative risk are absent from the STS algorithm (e.g., liver disease, frailty, porcelain aorta, previous chest radiation and neurocognitive dysfunction). Due to this limitation, both physician review of key clinical factors as well as quantitative assessments must be included in establishing approximate surgical risk.[124]

In The PARTNER Trial high-risk operable patients were considered for TAVR when presenting with severe AS and exhibiting NYHA class II or higher symptoms. STS scores were used as a guideline in establishing high-risk status, although clinicians at each site made the final determination.[6]

As described in detail in the Clinical Evidence section, in The PARTNER Trial, positive outcomes were reached for high-risk operable patients selected for TAVR versus surgical AVR. Among high-risk operable patients, rates of death in the TAVR group were 3.4% versus 6.5% in the surgical group at 30 days (p=0.07). At one year, mortality was 24.2% for the TAVR group and 26.8% for the surgical group (p=0.44) (p=0.001, noninferiority).[6] Results in the transfemoral arm of the Cohort A were better than the overall cohort. At 30 days, mortality was 3.3% vs. 6.2% for TF and AVR, respectively (p=0.07), and 22.2% vs. 26.4% for TF vs. AVR, respectively, (p=0.29) at one year. On this basis, the TF arm was also non-inferior to AVR (p=.002). As mentioned above, the transapical arm was not independently powered for statistical analysis.

Important but different adverse events were recorded in both of the study groups. At 30 days, TAVR patients experienced a higher incidence of major vascular complications (11.0% vs. 3.2%, p<0.001) and a higher incidence of adverse neurological events (5.5% vs. 2.4%, p=.04), but reported differences in major strokes (3.8% vs. 2.1%, p=0.20) were smaller and not statistically significant. Surgical patients experienced a higher incidence of major bleeding (9.3% vs. 19.5%, p<0.001) and new-onset atrial fibrillation (8.6% vs. 16.0%, p=0.006).[53]

The PARTNER Trial study represents the most reliable and valid outcomes to date for the high-risk operable patient population. Additionally, a review of the other pertinent literature on surgical outcomes in elderly high-risk patients also supports making TAVR available as a covered treatment option. As discussed above and summarized in *Table 4*, reported average survival rates for high-risk AVR at one, two and three years were 76%, 66%, and 58%, respectively. By comparison, the average reported survival rates in all TAVR series at one, two and three years are comparable, at 76%, 69% and 59%, respectively, despite including both high-risk and sicker inoperable patients. Based on this experience, TAVR coverage is provided by health systems in many countries including France, Germany, Italy and the UK for qualifying patients at high operative risk.

3. Future FDA Indications

In addition to coverage for high-risk and inoperable patients, we also support the Requestors' recommended coverage for additional indications that FDA may approve in the future. TAVR is a rapidly developing technology. There are many additional clinical studies underway and additional proposed indications for TAVR are likely to come before the FDA in the coming years. The Requestors' recommended approach would help ensure that in the future additional Medicare patients could quickly benefit from improved iterations of this less-invasive approach after they are determined to be safe and effective by the FDA.

We would suggest one modification to Requestors' language in this regard. We recommend that any FDA-specific language in a TAVR NCD reference FDA-approved "indications," not the broader term "labeling." This should help avoid confusion at the provider and contractor level.

Finally, after discussion with the Requestors, we recommend modifications within two areas of the Requestors' recommended list of nationally non-covered indications. Instead of the current language in Section C.1.f. regarding life-expectancy, we suggest the following alternative language: "the surgeon and cardiologist concur that a patient with significant, non-cardiac comorbidities will not benefit from the intervention." Secondly, with regard to the recommended exclusion of patients with untreated clinically significant coronary heart disease requiring revascularization, contained in Section C.1.c., we are aware of situations where high-risk or inoperable patients may be in need of both coronary artery revascularization and TAVR, and it may not be prudent to subject the patient to two separate hospitalizations. We would recommend striking this exclusion and providing coverage in these circumstances, while also continuing to study these procedures via analysis of registry data.

4. Coverage for Category B IDE Trials

In addition to the above covered patient populations, and to support ongoing future research on TAVR, Edwards also recommends and supports the Requestors' proposal that all indications studied under an approved Category B IDE clinical trial or other qualifying clinical study be covered by Medicare.

B. Facility Requirements

Edwards supports evidence-based facility requirements that will ensure that each TAVR procedure is performed in an optimal care setting that promotes patient safety and successful clinical outcomes. Edwards also supports performance of TAVR in facilities that are experienced and competent in performing the required patient evaluation, the TAVR procedure, and the follow-up care necessary to ensure optimal patient outcomes. As such, we agree with much of the Requestors' proposed NCD language with respect to facility requirements, with some specific modifications.

For each hospital adopting a TAVR program, Edwards supports the creation of a formal internal oversight committee responsible for granting TAVR operator privileges and for monitoring the quality of the individual clinicians, the care settings, and the program as a whole. The criteria listed below have proven to be important components of a successful TAVR program where the Edwards SAPIEN THV is implanted outside the US.

Establishment of a formal oversight committee to manage the introduction of a new technology is a model previously supported by CMS in coverage policy.[125] The facility oversight committee must determine site requirements to establish and maintain a TAVR program, utilizing existing evidence-based guidelines and recommendations. Facilities must have necessary imaging equipment, device inventory, staffing, and infrastructure to support a dedicated TAVR program. Specifically, facilities must provide the following:

- Immediate availability of transthoracic and transesophageal echocardiography
- Availability of a modified cardiac catheter laboratory as well as an operating room or a hybrid operating theater
- Appropriate fluoroscopy equipment for adequate visualization and guidance of the TAVR procedures
- CT scanning facilities for pre- and post-operative evaluation
- Pacing equipment
- Immediate availability of perfusion services in case of the need for bypass, including ability to provide extracorporeal circulation
- Technical capacities for interventional cardiology and cardiac surgery in case emergency conversion to AVR becomes necessary
- Onsite availability of a surgical recovery area and intensive care with staff experienced in caring for patients who have undergone valve replacement therapy

Edwards also believes that each facility should have in place a specific, dedicated multidisciplinary heart team, led by cardiac surgeons and cardiologists, that is responsible for evaluating, treating, and managing each patient eligible for TAVR. The heart team also should include echocardiography, an imaging specialist and anesthesiology. Each institution also should maintain written documentation regarding guidelines created by the oversight committee that, at minimum, meet the requirements described above.

TAVR guidelines created by CMS or the facility oversight committees should rely on evidence-based predictors of outcomes. As such, an annual minimum TAVR case volume requirement for hospitals should not be considered at this time. The annual Medicare TAVR case demand has not been determined, nor has there been any clearly established correlation between TAVR case volumes and outcomes. Rather, the evidence is mixed on this point. As with many transformational technologies, some evidence suggests that there is a necessary learning curve that operators must navigate to become proficient in TAVR.[83,126,127] However, in several studies that have examined this question broadly, across centers, no correlation was found in procedural success between high and low TAVR volume hospitals.[59,102] Experienced observers have noted that good initial outcomes are as much a function of good training and collaboration between members of a dedicated heart team, as they are of operator or institution procedural volumes.[59] Accordingly, the Edwards experience has led us to a site-selection process that includes an extensive selection criteria designed to optimize patient outcomes. This was evidenced in The PARTNER Trial, where observed mortality rates were the lowest to date in any large, multi-center TAVR study, despite wide variation in site volumes and the investigators own acknowledgment that experience with the procedure was limited.[3,6,53]

Similarly, while there has been discussion about the potential use of other surgical or percutaneous coronary intervention (PCI) case volume thresholds as a proxy requirement for TAVR regional centers, we believe the use of such a requirement would also be inappropriate. While some of the pre and post-operative requirements for surgical AVR and PCI cases may be similar to those required for TAVR cases, the procedures are fundamentally different. Moreover, the literature on the relationship between surgical and interventional cardiology center volume and outcomes is mixed. A recent study of various surgical interventions in the Medicare population, found no correlation between hospital AVR procedural volume and outcomes.[128§§§] Similarly, new data indicates that, within interventional cardiology, as well as with other surgical interventions, volume alone is not a consistent predictor of quality outcomes.[129-132]

Should CMS contemplate requiring minimum hospital or operator TAVR case volumes, we would note that such requirements could, depending on their severity, restrict appropriate patient access to this important new therapy by significantly limiting the number of hospitals providing TAVR. Rather, with committed teams of interventional cardiologists and surgeons who are dedicated to optimizing outcomes, and with the proper provider training and institutional facility requirements, we believe an appropriate number of implanting centers will be available to ensure appropriate access for this sick and frail patient population.

Finally, we note that the Requestor's submission recommends that Medicare coverage policy incorporate a future (currently unpublished) clinical treatment guideline for TAVR into its substantive requirements for hospitals and physicians who seek to perform Medicare-covered procedures. While we welcome and encourage the societies' ongoing efforts to develop guidelines (and possibly related credentialing or accreditation programs), we believe these efforts should be advisory but not binding on

§§§ Even in Birkmeyer, J. D. , T.A., Stukel , et. al., Surgeon volume and operative mortality in the United States., *N Engl J Med* 2003;349:2117-2127., cited by the Requestors, the authors note that surgeon volume is more closely associated with improved outcomes than hospital volume.

the Agency. Rather, to the extent CMS agrees with such recommendations and wants to require them, it should do it directly in the NCD (after the requisite period for public review and comment during the NCA process). Similarly, we fully expect that hospitals will incorporate appropriate treatment guidelines into their administrative and credentialing practices.

C. Provider Training and Credentialing

Edwards Lifesciences is committed to providing and assuring a comprehensive training program to all prospective TAVR sites. To date, Edwards has conducted over 125 training sessions, 2,000 hours of didactic training, and hosted over 3,500 proctored cases for the over 400 hospitals offering this technology around the world. Training and the ongoing sharing of learnings across the global medical community have been crucial for the consistently positive TAVR outcomes. Given that TAVR is a new procedure in the US, appropriate training is a required and essential element of successful development and introduction into the health care delivery system.

Consequently, Edwards has devoted substantial time and resources to its physician training program. Prior to selling a transcatheter valve in the US, Edwards will require a prospective site to commit to the training and development of a dedicated heart team to oversee all TAVR procedures. The company will not proceed to the next steps of the training program until the site confirms that the heart team is in place.

The Edwards THV US training program will include didactic instruction, procedural simulation, proctoring, and on-going support. After an initial meeting with the hospital's heart team to review the training manual and specific imaging and patient selection pre-training videos, the procedural heart team attends a formal two-day training at one of our training centers. The two-day training focuses on screening a minimum of five cases (including operative assessment, echo, and vascular screening), step-by-step case management and the operative decision-making process. Next, the focus turns to procedural training through a systematic review of procedural steps, peri-operative decision making, and potential complications.

Training provides hands-on sessions with device demonstrations and simulation training, with extensive time spent on complication detection and mitigation. Procedural simulation is a key part of our program. The simulators are custom designed for the Edwards SAPIEN program and allow the physician to practice each step of the procedure. This sophisticated simulation captures critical metrics such as proper device placement, hemodynamic status, contrast usage and other key clinical parameters.

After successful completion of the two day training course, the heart team moves to the proctor phase. Experienced physician proctors remain on site until the heart team is comfortable performing the procedure, and the proctor and Edward's clinical team has confirmed that the site is ready to be proctor independent.

After the proctoring phase is complete, the heart team is supported by the Edwards Field Clinical Specialists, who stay on site for a minimum of 20 cases after proctoring and remain available as needed

for all cases. Additionally, we provide 24 hour support, and continuing education and training updates through a designated web portal.

While Edwards fully supports additional efforts, including society-led initiatives, to educate clinicians about the use of TAVR, we believe it is best and most appropriate for hospitals to retain the primary responsibility for credentialing their operators. Historically, CMS has deferred individual state licensing boards and to the hospital privileging process when determining which procedures a health care professional can perform. We see no reason to deviate from that practice with TAVR.

To the extent that medical societies develop TAVR-specific additions to curricula, continuing medical education or other educational opportunities, we feel confident that hospital credentialing bodies will take these into account when credentialing physicians and developing their protocols. In an effort to inform and make these efforts as comprehensive as possible, we are actively sharing with all interested medical societies our experience in training physicians on the TAVR procedures used with the Edwards SAPIEN THV.

D. Data Collection

Edwards supports ongoing data collection on TAVR to better understand and improve outcomes. We are actively engaged in additional US and global clinical research with respect to TAVR. We have also agreed with the FDA to rigorous post-approval data collection requirements that will evaluate the safety and effectiveness of the SAPIEN THV in the commercial setting, as well as provide long-term follow-up data on all patients. In addition, we are working with the Requestors on their proposal for a national transcatheter valve registry. To help support this effort, we believe Medicare's coverage policy for TAVR should require patients receiving transcatheter valves to be enrolled in a registry or have related procedural data collected and analyzed as part of an ongoing Category B IDE or other clinical study covered by Medicare where relevant. Similarly, to avoid unnecessary expense and limits on future research, we would recommend, as we have discussed with the Requestors, that data in qualifying registries be subject to established auditing standards, rather than data adjudication (Section B.1.a).

We appreciate the Requesters' inclusion of proposed Coverage with Evidence (CED) language in their recommended NCD (Section D). We believe that improvements should be made here to clarify that data collected as part of a registry or as part of an ongoing Category B IDE or other clinical study covered by Medicare will satisfy the standing data collection requirements of Medicare's CED policy. Similarly studies utilizing such data should be sufficient to meet CMS's CED coverage requirements. As discussed with the Requestors, we also recommend improving their CED proposal by expanding the covered clinical circumstances to include "valve in valve" and studies including End-Stage Renal Disease (ESRD) patients.

In summary, like the Requestors', Edwards supports the provision of TAVR coverage for both inoperable and high-risk operable patients. We also share the Requestors' support for the use of a dedicated, multidisciplinary heart team, led by an interventional cardiologist and a cardiac surgeon, to appropriately select and manage all TAVR patients. To faciliatate the heart team concept, and support patient-centric treatment strategies, we believe it is essential that any TAVR NCD provide coverage for

both the transfemoral and transapical approaches. To ensure the best possible outcomes, we also agree that TAVR should be provided in appropriately equipped hospitals, and that patient selection and treatment decision-making should rely on active and ongoing collaboration of the heart team. This process must utilize pre-screening imaging to assess vasculature suitability for the possible use of a transfemoral approach, and ongoing consultation across the heart team to ensure that each individual patient's unique co-morbidities, anatomical characteristics and specific operative risk are considered before deciding on the best possible treatment approach. In addition, we support ongoing research on TAVR via data collection on all future Medicare-covered TAVR implants, and through the authorization of the targeted CED provisions.

However, for the reasons discussed above, Edwards believes the that following modifications, which we have discussed with the Requestors, should be made to the Requestors' proposed NCD language:

- Change "FDA-approved labeling." to "FDA-approved indications."
- Remove the sentence – "Specifically, the probability of death or serious irreversible morbidity should exceed 50%." – since it is redundant and is unnecessary.
- Change "adjudicated" to "audited" in the National TVT Registry section.
- Remove the non-covered indication for patients with significant CAD requiring revascularization
- Remove specific non-covered indication referencing life-expectancy and replace with "The surgeon and cardiologist concur that a patient with significant, non-cardiac comorbidities will not benefit from the intervention."
- Clarify the CED data collection requirements by inserting the words (underlined) in the first sentence: "TAVR is only covered under CED <u>when utilizing the National TVT Registry data elements to address one or more of the</u> following clinical circumstances".
- Amend CED provisions to include studies on TAVR for "valve in valve" and end-stage renal disease (ESRD) patients.

V. <u>Conclusion</u>

A substantial body of evidence supports a national coverage determination that provides coverage for TAVR for Medicare beneficiaries diagnosed with severe symptomatic aortic stenosis who are determined by a dedicated, multi-disciplinary heart team to be inoperable or at high operative risk. Coverage for both transfemoral and transapical approaches will provide heart teams the ability to choose patient-centric treatment strategies that account for each patient's unique health and anatomical needs. To ensure ready access for this very sick population, coverage should be provided at institutions that meet the appropriate facility requirements specified above. Medicare TAVR coverage policy should also promote ongoing research by requiring the ongoing collection of all TAVR-related procedural data via a registry, a Medicare covered Category B IDE or other clinical study.

The Requestors' proposed NCD language provides a sound basis for CMS coverage policy, if modified as specifically described above and if the societies' future "consensus document" remains advisory to the CMS process. Edwards looks forward to working closely with CMS throughout the NCD process and to providing any additional information that may be required.

VI. Appendices

A. Appendix A: Overview of Literature Search Strategy

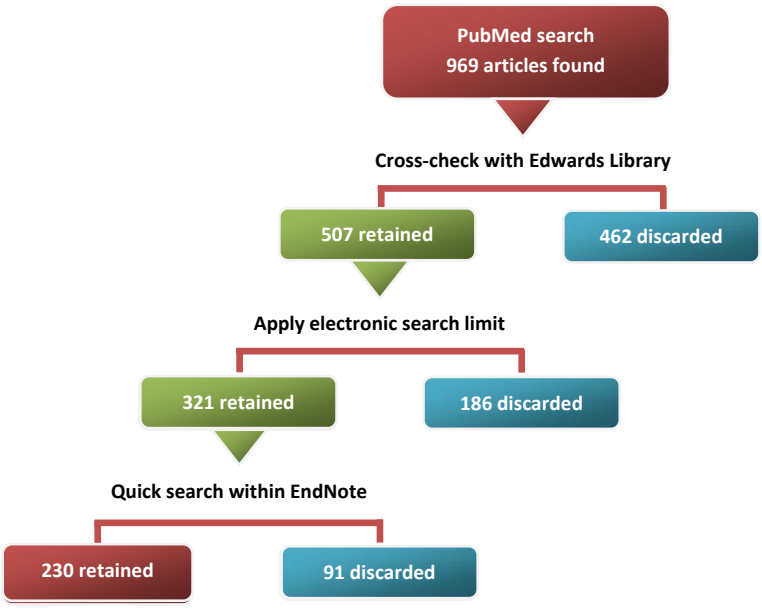
TAVR literature search

For the TAVR literature review, a PubMed search within the EndNote program was performed in May 2011, using the specific terms and combinations to yield the results in *Table 7*. After May, we continued to review publications using an automated PubMed literature search that was performed weekly using similar search terms. Articles identified through this process, as well as through hand-searching bibliographies and relevant medical conference presentations, were also considered.

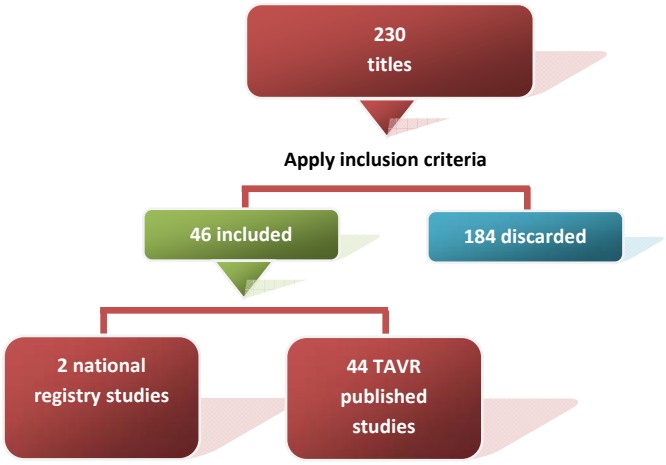
Table 7: TAVR Literature Search Results

Number	Search Terms	Results
1	Transcatheter aortic valve	707
2	TAVR (NOT author: TAVR)	252
3	TAVR	10
	Total	969

Electronic limits were subsequently applied to restrict the results only to articles in English, published on or after 2005, and containing abstracts. A quick search within EndNote using the terms "aortic" and "review" facilitated the filtering of articles. Studies that dealt with aortic valve procedures were retained and reviews were discarded. This process is presented below:



Furthermore, the inclusion criteria consisted of a patient population with severe aortic stenosis and that is undergoing the TAVR procedure. Studies reviewed were only clinical in design, either observational or interventional, and the outcomes listed in *Table 1* dictated those studies that would be retained for review. The following flowchart displays the described process:



The main reasons for exclusion were: not aortic valve; technical in nature (ie, research and development), reviews; editorials; letters; case reports; not relevant patient population; subpopulation of a study cohort in an included article; small sample; and no survival data. NOTE: 10 additional studies were identified after May 2011, and 1 article captured in the initial search was subsequently excluded as a redundant patient cohort. This brings the total number of TAVR articles included in the clinical overview section to 55.

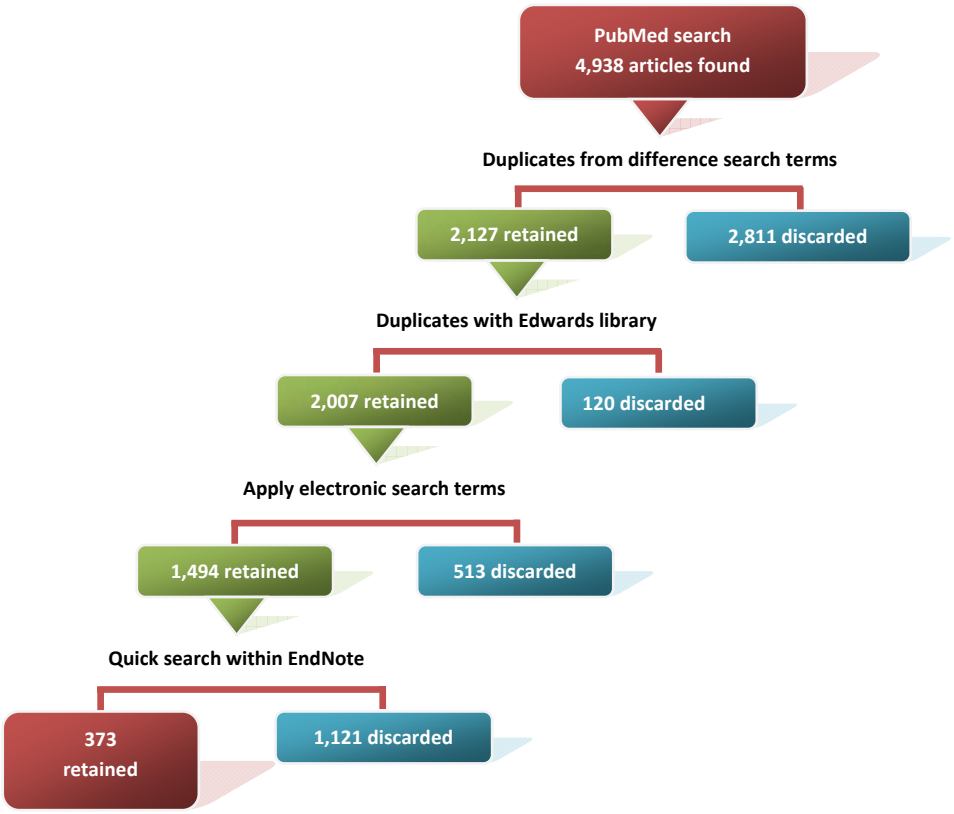
Non-TAVR literature search

A similar process was carried out for the non-TAVR literature search. For the literature review, a PubMed search within the EndNote program was implemented using the specific terms and combinations to yield the results in *Table 8*. After May, we continued to review publications using an automated PubMed literature search that was performed weekly using similar search terms. Articles identified through this process, as well as through hand-searching biobliographies and relevant medical conference presentations, were also considered.

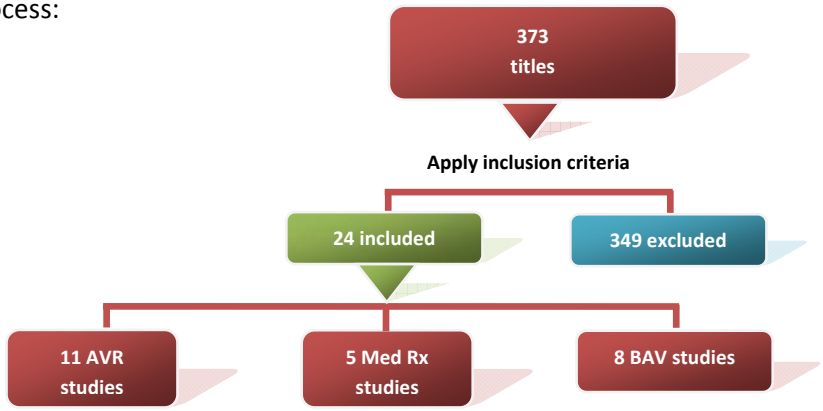
Table 8: Non-TAVR Literature Search Results

Number	Search Terms	Results
1	Aortic stenosis AND management NOT transcatheter aortic valve NOT TAVR	2,014
2	Aortic stenosis AND management AND (aortic valve replacement or AVR or aortic valve surgery)	1,141
3	Aortic stenosis and management AND (therapy OR unoperated OR conservative OR nonsurgical OR valvuloplasty)	4,938
	Total	4,938

Electronic limits were subsequently applied to restrict the results to articles only in English, published on or after 1989, and that contain abstracts. A quick search within EndNote using the terms "mortality" OR "survival" OR "death," and the term "review" facilitated the filtering of articles. Studies that contained survival/mortality outcomes were retained and reviews were discarded. This process is presented below:



The inclusion criteria consisted of a high-risk patient population with severe symptomatic aortic stenosis undergoing any of the following interventions: AVR, medical management, and/or BAV. Studies reviewed were only clinical in design, either observational or interventional, and the outcomes listed in *Table 1* dictated those studies that would be retained for review. The flowchart below displays the described process:



The main reasons for exclusion were: disease was not severe symptomatic aortic stenosis; articles were reviews, editorials and letters; not relevant patient population; no mortality or survival data; different technology; and case reports. Note: several additional publications and medical conference presentations were identified after May 2011, or through a hand-search of bibliographies and medical conference presentations. This brings the total number of relevant AVR and medical management studies to 13 and 15, respectively.

Duplicative patient cohorts were eliminated when possible; however, there is still likely to be some overlap across studies. In limited circumstances, duplicative patient cohorts were intentionally included when there were other compelling reasons to do so; such as when subset analyses provided longer term follow up or when the results presented other comparisons of interest.

B. Appendix B: Reference Tables

Table 9: Feasibility studies initiated by Edwards Lifesciences

Trial	N	Profile	Survival		
			30 day	6 months	12 months
Revive II TF or TA[xiii]	106	Age 84 y Log ES 29%	87%	79%	73%
Revival II TF[68]	55	Age 83 y Log ES 34% STS 13%	93%	84%	76%
Revival II TA[70]	40	Age 83 y Log ES 36% STS 13%	82%	59%	--
TRAVERCE TA[71]	168	Age 82 y Log ES 27%	85%	70%	63%
PARTNER EU TF[69]	61	Age 82 y Log ES 26% STS 11%	92%	90%	79%
PARTNER EU TA[69]	69	Age 82 y Log ES 34% STS 12%	81%	58%	49%

Table 10: The US PARTNER Trial - Clinical Outcomes: (Cohort B)

	30 Days			1 Year		
Outcome	TAVR (n = 179)	Standard Therapy (n = 179)	P value	TAVR (n = 179)	Standard Therapy (n = 179)	P value
All-Cause Mortality	5%	2.8%	0.4	30.7%	50.7%	<0.001
Repeat Hospitalization	5.6%	10.1%	0.17	22.3%	44.1%	<0.001
Death or Repeat Hospitalization	10.6%	12.3%	0.74	42.5%	70.4%	<0.001
All Stroke or TIA	6.7%	1.7%	0.03	10.6%	4.5%	0.04
Major Stroke	5.0%	1.1%	0.06	7.8%	3.9%	0.18
Death or Major Stroke	8.4%	3.9%	0.12	33.0%	50.3%	0.001
Major Vascular Complications	16.2%	1.1%	<0.001	16.8%	2.2%	<0.001
Renal-Replacement Therapy	1.1%	1.7%	1.00	1.7%	3.4%	0.50
Major Bleeding	16.8%	3.9%	<0.001	22.3%	11.2%	0.007
New Atrial Fibrillation	0.6%	1.1%	1.00	0.6%	1.7%	0.62
New Pacemaker	3.4%	5.0%	0.60	4.5%	7.8%	0.27

[xiii] Unpublished data

Table 11: The US PARTNER Trial - Echocardiographic Findings[xiv]: (Cohort B)

	30 Days			1 Year		
Outcome	TAVR (n = 179)	Standard Therapy (n = 179)	P value	TAVR (n = 179)	Standard Therapy (n = 179)	P value
Mean Gradient (mmHg)	11.4 ± 7.0	33.1 ± 12.6	NA	13.2 ± 11.2	44.3 ± 16.1	NA
AVA (cm^2)	1.5 ± 0.4	0.8 ± 0.2	NA	1.6 ± 0.5	0.7 ± 0.3	NA
LV Ejection Fraction (%)	57.9 ± 10.1	51.7 ± 13.9	NA	57.2 ± 10.6	56.9 ± 10.3	NA
Paravalvular AR – moderate / severe	12%	0%	NA	11%	0%	NA

Table 12: The US PARTNER Trial - Clinical Outcomes: (Cohort A)

	30 Days			1 Year		
Outcome	TAVR (n = 348)	AVR (n = 351)	P value	TAVR (n = 348)	AVR (n = 351)	P value
All-Cause Mortality	3.4%	6.5%	0.07	24.2%	26.8%	0.44
Repeat Hospitalization	4.4%	3.7%	0.64	18.2%	15.5%	0.38
Death or Repeat Hospitalization	7.2%	9.7%	0.24	34.6%	35.9%	0.73
All Stroke or TIA	5.5%	2.4%	0.04	8.3%	4.3%	0.04
Major Stroke	3.8%	2.1%	0.20	5.1%	2.4%	0.07
Death or Major Stroke	6.9%	8.2%	0.52	26.5%	28.0%	0.68
Major Vascular Complications	11%	3.2%	<0.001	11.3%	3.5%	<0.001
Renal-Replacement Therapy	2.9%	3.0%	0.95	5.4%	6.5%	0.56
Major Bleeding	9.3%	19.5%	<0.001	14.7%	25.7%	<0.001
New Atrial Fibrillation	8.6%	16.0%	0.006	12.1%	17.1%	0.07
New Pacemaker	3.8%	3.6%	0.89	5.7%	5.0%	0.68

Table 13: The US PARTNER Trial - Echocardiographic Findings[xv]: (Cohort A)

	30 Days			1 Year		
Outcome	TAVR (n = 348)	AVR (n = 351)	P value	TAVR (n = 348)	AVR (n = 351)	P value
Mean Gradient (mmHg)	9.9 ± 4.8	10.8 ± 5.0	0.04	10.2 ± 4.3	11.5 ± 5.4	0.008
AVA (cm^2)	1.7 ± 0.5	1.5 ± 0.4	0.001	1.6 ± 0.5	1.4 ± 0.5	0.002
LV Ejection Fraction (%)	55.5 ± 11.4	56.0 ± 11.4	0.63	56.6 ± 10.5	57.1 ± 10.3	0.64
Paravalvular AR – moderate / severe	12.2%	0.9%	<0.001	6.8%	1.9%	<0.001

[xiv] Reprinted from supplementary appendix of Leon et al. *NEJM* 2010

[xv] Reprinted from supplementary appendix of Smith et al. *NEJM* 2011

Table 14: SOURCE Registry outcomes of Cohort 1 and Cohort 1 & 2 pooled analysis

30 day Outcomes	Cohort 1[55]		Cohort 1 & 2[117]	
	TF (n = 463)	TA (n = 575)	TF (n = 920)	TA (n = 1387)
All-Cause Mortality	6.3%	10.3%	7.5%	10.9%
Stroke	2.4%	2.6%	2.9%	2.5%
Myocardial infarction	NA	NA	0.9%	0.5%
Conversion to open AVR	1.7%	3.5%	1.0%	0.6%
Vascular Access- Complications	17.9%	2.4%	--	--
Major Vascular Access and Nonaccess Complications	10.6%	2.4%	11.3%	2.0%
Valve-in-Valve	0.6%	3.3%	0.3%	2.2%
Renal-Replacement Therapy	1.3%	7.1%	1.8%	6.7%
AR > grade 2+	1.5%	2.3%	--	--
New Pacemaker	6.7%	7.3%	6.7%	7.1%

Table 15: Other TAVR Observational studies

Reference	Approach	Characteristics	N	Survival				
				30d	6m	1 year	2 year	3 year
Aktug et al. 2011[103]	TF/TA	Age 81, "High or prohibitive risk"	154	88%	--	--	--	--
Aregger et al. 2009[60]	TF/TA	Age 83, Log ES 27%	58	93%	--	--	--	--
Attias et al. 2010[61]	TF	Age 81, Log ES 26%, STS 15%	83	93%	--	78%	71%	--
Bagur et al. 2009[104]	TF/TA	Age 82, Log ES 29%	213	90%	--	--	--	--
Bleiziffer et al. 2009[105]	TF/TA	Age 81, Log ES 22%, STS 6%	203	90%	78%	--	--	--
Bleiziffer et al. 2011[106]	TA	Age 80, Log ES 21%, STS 6%	143	90%	78%	76%	--	--
Buz et al. 2011[62]	TA	Age 77, Log ES 45%, STS 23%	46	100%	88%	85%	--	--
Clavel et al. 2010[63]	TF/TA	Age 81, Log ES 32%, STS 12%	83	81%	--	--	--	--
Conradi et al. 2010[64]	TF/TA	Age 80, Log ES 27%, STS 9%	28	93%	--	--	--	--
Covello et al. 2010[65]	TF/TS	Age 79, Log ES 27%	69	100%	86%	--	--	--
Cribier et al. 2006[74]	TF	Age 80, Additive ES 12%	36	78%	63%	--	--	--
Drews et al. 2010[75]	TA*	Age 79, Log ES 40%, STS 23%	198	93%	78%	76%	65%	--
Dworakowski et al. 2010[76]	TF/TA*	Age 83, Log ES 22%	151	90%	--	76%	--	--
Elhmidi et al. 2011[107]	TF/TA/TS/Taortic*	Age 81, Log ES 21%, STS 6%	234	91%	82%	--	--	--
Ewe et al. 2011[78]	TF/TA	Age 81, Log ES 21%, STS 9%	104	90%	87%	83%	--	--
Ewe et al. 2010[77]	TF/TA*	Age 81, Log ES 22%	147	93%	89%	85%	--	--
Ferrari et al. 2010[79]	TA	Age 80, Log ES 32%	30	90%	--	--	--	--
Fusari et al. 2009[80]	TF/TA	Age 80, Log ES 30%	22	95%	--	--	--	--
Godino et al. 2009[81]	TF/TA/TAx*	Age 79, Log ES 27%, STS 7%	137	98%	86%	--	--	--
Gurvitch et al. 2010[67]	TF/TA	Age 85, Log ES 32%, STS 10%	70	--	--	81%	74%	61%
Hernandez-Antolin et al. 2011[82]	TF	Age 83, Log ES 18%, STS 6%	76	84%	--	76%	--	--
Himbert et al. 2009[83]	TF/TA*	Age 82, Log ES 26%, STS 16%	75	90%	--	78%	--	--
Jahangiri et al. 2011[108]	TF/TA/SC	Age 82, Log ES 14%, STS 13%	63	100%	--	83%	--	--
Johansson et al. 2011[109]	TF/TA*	Age 81, Log ES 24%	40	95%	77%	77%	--	--
Kahlert et al. 2009[84]	TF	Age 80, Log ES 22%	60	88%	--	--	--	--
Kempfert et al. 2010[85]	TA	Age 79, Log ES 38%, STS 13%	29	83%	--	--	--	--

Reference	Approach	Characteristics	N	Survival				
				30d	6m	1 year	2 year	3 year
Lange et al. 2011[110]	Tart/TA*	Age 80, Log ES 20%, STS 6%	412	91%	79%	77%	--	--
Mussardo et al. 2011[86]	TF*	Age 80, Log ES 25%, STS 7%	120	98%	--	--	--	--
Pasic et al. 2010[57]	TA	Age 80, Log ES 38%, STS 24%	175	95%	86%	83%	--	--
Rodes-Cabau et al. 2011[87]	TF/TA	Age 79, STS 8%	101	94%				
Tamburino et al. 2011[88]	TF/TA	Age 81, Log ES 22%, STS 7%	165	91%	--	82%	--	--
Taramasso et al. 2011[111]	TF/TA/TAx*	Age 79, Log ES 28%, STS 22%	177	97%	85%	--	--	--
Tchetche et al. 2010[89]	TF	Age 82, Log ES 25%	45	98%	--	--	--	--
Thielmann et al. 2009[90]	TF/TA*	Age 81, Log ES 44%, STS 18%	39	82%	74%	64%	--	--
Walther et al. 2011[94]	TA	Age 82, Log ES 31%, STS 12%	299	91%	--	73%	68%	58%
Walther et al. 2010[112]	TA	Age 83, Log ES 31%, STS 15%	100	90%	75%	73%	--	--
Walther et al. 2007[113]	TA	Age 81, Log ES 27%	59	86%	--	--	--	--
Witkowski et al. 2011[91]	TF/TA/SC	Age 82, Log ES 29%	30	93%	--	--	--	--
Ye et al. 2010[72]	TA	Age 80, Log ES 35%, STS 12%	71	83%	74%	72%	66%	58%
Zhao et al. 2011[92]	TA	Age 79, Log ES 19%, STS 17%	20	100%	--	--	--	--
Zierer et al. 2009[93]	TA	Age 85, Log ES 38%	21	86%	--	76%	--	--
*Calculated weighted average			**Mean**	**91%**	**80%**	**78%**	**69%**	**59%**

Table 16: Alternative treatments - survival with medical management and/or BAV[xvi]

Reference	Therapy	Characteristics	N	Survival				
				30d	6m	1 year	2 year	3 year
Pedersen et al. 2007[50]	BAV	Age >90, Log ES 36%, STS 19%	31	90%	--	--	--	--
To et al. 2008[22]	BAV	Age 87, Log ES 26%	26	100%	88%	64%	31%	--
Dewey et al. 2008[14]	Med Rx	Age 81, Log ES 31%, STS 11%	52	86%	58%	51%	42%	--
	BAV	Age 78, Log ES 33%, STS 12%	16	87%	52%	52%	--	--
Sack et al. 2008[21]	BAV	Age 78, Log ES 24%	75	--	70%	60%	--	--
Otten et al. 2008[17]	Med Rx	Age 82, Log ES 25%	16	--	70%	40%	--	--
Kojodjojo et al. 2008[16]	Med Rx	Age 87, Log ES 20%	62	85%	55%	51%	26%	10%
Kapadia et al. 2009[15]	Med Rx	Age 83, Log ES 25%, STS 12.6%	36	--	--	58%	--	--
Don et al. 2010[19]	BAV	Age 87, Log ES 37%	73	94%	--	--	--	--
Yamen et al. 2010[23]	BAV	Age 79, STS 13%	20	95%	73%	63%	--	--
Kapadia et al. 2010[20]	BAV	Age 75, "inoperable"	90	83%	57%	44%	--	--
Schueler et al. 2010[18]	Med Rx	Age 88, Log ES 29%, STS 11%	79	--	71%	66%	42%	--
Ben-Dor et al. 2010[13]	MedRx/BAV	Age 81, Log ES 42%, STS 13%	274	90%	68%	60%	47%	--
Leon et al. 2010[3]	Med Rx/BAV	Age 83, Log ES 31%, STS 12%	179	97%	--	49%	--	--
Jahangiri et al. 2011[108]	Med Rx	Age 82, Log ES 14%, STS 15%	38	--	--	70%	--	--
Clark et al. 2011[12]	Med Rx	Age 85, Log ES 34%	651	--	--	42%	24%	14%
			Mean	**91%**	**66%**	**55%**	**35%**	**12%**

[xvi] In some instances, survival estimates were derived from Kaplan-Meier curves when absent in the text

Table 17: Alternative treatments - survival in high-risk patients receiving AVR[xvii]

Reference	Characteristics	N	Survival				
			30d	6m	1 year	2 year	3 year
Jamieson et al. 1999[133]	STS ≥ 10	1520	82%	--	--	--	--
Collart et al. 2005[134]	Age 83, Log ES 34%	62	87%	--	--	--	--
Dewey et al. 2008[135]	Age 78, Log ES 33%, STS 8%	97	85%	73%	71%	65%	61%
Wendt et al. 2009[136]	Age 76, Log ES 29%, STS 10%	52	96%	--	90%	85%	--
Kalavrouziotis et al. 2009[35]	Age 73, Log ES 39%	237	89%	--	81%	--	69%
Leontyev et al. 2009[36]	Age 84, Log ES 33%	72	90%	85%	69%	64%	56%
Zierer et al. 2009[93]	Age 82, Log ES 35%	30	90%	--	83%	--	--
Florath et al. 2010[137]	Age 84, Log ES 24%, STS 13%	95	88%	77%	69%	64%	56%
Walther et al. 2010[112]	Age 82, Log ES 30%	100	85%	70%	69%	--	--
Thourani et al. 2011[34]	Age 76, STS 16%	159	84%	--	71%	--	57%
Jahangiri et al. 2011[108]	Age 80, Log ES 14%, STS 14%	74	100%	--	96%	--	--
Clark et al. 2011[119]	Age 78, Log ES 37%	252	--	--	60%	54%	47%
Smith et al. 2011[53]	Age 85, Log ES 29%, STS 12%	351	94%	--	73%	--	--
		Mean	**89%**	**76%**	**76%**	**66%**	**58%**

[xvii] In some instances, survival estimates were derived from Kaplan-Meier curves when absent in the text

C. Appendix C: Evidence Tables

Table 18: Published TAVR studies

Reference	Study design	Valve / Access	Number of patients / Baseline characteristics	Procedural success	Effectiveness Mean gradient (mmHg)	Mean aortic valve area (cm2)	Mean LVEF (%)	NYHA class	Survival	Major early complications	Length of stay/ Remarks
					Feasibility Studies						
North America											
Svensson et al. 2008[70]	Prospective, feasibility multicenter study Enrollment: 2006 - 2008	Edwards SAPIEN TA	N = 40 Age: 83 Log ES: 35.5% STS: 13.4%	100% (technical success)	*Baseline* 40.2 ± 9.8 *30d* 7.7 ± 2.5 *6m* 7.4 ± 2.4	*Baseline* 0.62 ± 0.12 * *30d* 1.61 ± 0.37 * *6m* 1.49 ± 0.24 * * reflects EOA	*Baseline* 51.5 ± 15.1 *30d* 55.0 ± 19.2 *6m* 58.0 ± 16.7	*Baseline* 3.33 ± 0.47 *30d* 2.25 ± 0.79 *6m* 2.08 ± 0.51	*30d* 81.8% *6m* 58.7%	Conversion: 5% MI: 15% Stroke: 5% Valve embolization: 0% MACCE: 35%	QoL scores (SF-12) improved between pre-op time and 6 months
Kodali et al. 2011[68] REVIVAL Trial	Prospective, multi-center, first series in the United States Enrollment: 2005-2006	Cribier-Edwards TF	N = 55 Age: 82.8 Log ES: 33.5% STS: 13.0%	87%	*Baseline* 44.7 ± 16.3 *Post-operative* 10.7 ± 5.0	*Baseline* 0.57 ± 0.14 *Post-operative* 1.6 ± 0.48	*Baseline* 50.9 ± 17.2 *30d* 56.2 ± 13.8	*Baseline* ≥ III: 87% 3.22 ± 0.66 *12m* < III: 89.7% 1.50 ± 0.85	*30d* 92.7% *6 m* 84% *12 m* 76.4%	Cerebrovascular accident (major): 4% MI: 4% Vascular complications: 13% Structural valve deterioration: 0%	
Europe											
Walther et al. 2010[71] TRAVERCE TA feasibility Trial	Prospective, multicenter Enrollment: 2006 – 2008	Cribier Edwards or Edwards SAPIEN TA	N = 168 Age: 82.1 Los ES: 27%	95.8%	*Baseline* 43 ± 17 *Post-operative* 8 ± 4	*Baseline* 0.6 ± 0.2 *Post-operative* 1.5 ± 0.5	*Baseline* 53 ± 16 *Post-operative* 52 ± 15	≥ III: 97%	*30d* 85% *6m* 70% *12m* 63%	MI: 1% Stroke: 2% Explant: 4% SVD: 0%	No reports of SVD at last follow-up

Reference	Study design	Valve / Access	Number of patients / Baseline characteristics	Procedural success	Effectiveness Mean gradient (mmHg)	Mean aortic valve area (cm2)	Mean LVEF (%)	NYHA class	Survival	Major early complications	Length of stay/ Remarks
Lefevre et al. 2010[69] PARTNER EU Study	Prospective, multicenter Enrollment: 2007 - 2008	Edwards SAPIEN TF TA	TF N = 61 Age: 82.3 Log ES: 25.7% STS: 11.3% TA N = 69 Age: 81.9 Log ES: 33.8% STS: 11.8%	TF: 96.4% TA: 95.4%	*Baseline* TF: 46.6 ± 17.3 TA: 47.2 ± 18.9 *6m* TF: 11.1 ± 3.7 TA: 10.6 ± 6.9 *12m* TF: 12.7 ± 4.8 TA: 11.5 ± 3.9	*Baseline* TF: 0.7 ± 0.2 * TA: 0.6 ± 0.2 * *6m* TF: 1.5 ± 0.4 * TA: 1.4 ± 0.4 * 12m TF: 1.5 ± 0.5 * TA: 1.6 ± 0.5 * * reflects EOA	*Baseline* TF: 53.2 ± 18.4 TA: 54 ± 13.8 *6m* TF: 56.2 ± 16.1 TA: 56.1 ± 14.8 *12m* TF: 56.3 ± 13.0 TA: 55.2 ± 8.2	*Baseline* > III TF: 83.6% TA: 85.5% *6m* > III TF: 10.9% TA: 10.0% *12m* > III TF: 10.4% TA: 14.7%	*30d* TF: 91.8% TA: 81.2% *6m* TF: 90.2% TA: 58% *12m* TF: 78.7% TA: 49.3%	Major access site complication: 8% Iliac perforation: 2% Femoral perforation: 1% Iliac artery stent thrombosis: 1%	No cases of structural valve dysfunction at follow-up were observed
Thielmann et al. 2009[90]	Prospective, single-center Enrollment: 2005 - 2008	Cribier Edwards or Edwards SAPIEN TF (38%) TA (62%)	TF N = 15 Age: 79.6 Log ES: 38.1% STS: 15.1% TA N = 24 Age: 82.7 Log ES: 52.5% STS: 19.9%	TF: 100% TA: 96%	*Baseline* 45.5 ± 19.8 * *Discharge* 12.0 ± 5.0 * *TF/TA pooled	*Baseline* 0.6 ± 0.2 *† *Discharge* 1.7 ± 0.6 *† *TF/TA pooled †EOA	*Baseline* TF: 48.8 ± 21.2 TA: 52.1 ± 12.8 *Discharge* 51.1 ± 16.9 * *TF/TA pooled	*Baseline* TF: 3.5 ± 1.7 TA: 3.3 ± 0.4 *Discharge* 1.6 * *TF/TA pooled	*30d* TF: 86.7% TA: 79.2% *6m* TF: 79.4% TA: 70.7% *12m* TF: 68.1% TA: 61.9%	Conversion TF: 0% TA: 4% Pacemaker TF: 27% TA: 0% TIA/Stroke TF: 7% TA: 0% Renal failure* TF: 20% TA: 8% * requiring transient dialysis	Mean ICU stay TF: 5 days TA: 2 days Mean total LOS TF: 11 days TA: 12 days
Walther et al. 2007[113]	Prospective, multicenter Enrollment: 2006 - 2006	Edwards SAPIEN TA	N = 59 Age: 81.4 Log ES: 26.8%	93.2%	*Post-operative* 9 ± 6	*Baseline* 0.5 ± 0.15	*Baseline* 47 ± 16	*Baseline* 3.4 ± 0.5	*30d* 86.4% *6m* 75.7%	Conversion: 6.8% Stroke: 3.4% Renal failure: 13.6%* * requiring transient hemofiltration	Median ICU stay: 20 hours

Reference	Study design	Valve / Access	Number of patients / Baseline characteristics	Procedural success	Effectiveness Mean gradient (mmHg)	Mean aortic valve area (cm2)	Mean LVEF (%)	NYHA class	Survival	Major early complications	Length of stay/ Remarks
Cribier et al. 2006[74]	Prospective, single-center, feasibility Enrollment: 2003 - unknown	Cribier Edwards TF	N = 36 Age: 80 Additive ES: 12%	82% (technical success)	*Baseline* 37 ± 13 *Post-operative* 9 ± 2	*Baseline* 0.6 ± 0.09 *Post-operative* 1.70 ± 0.11	*Baseline* 45 ± 18 *Post-operative* 53 ± 14	NA	*30d* 77.8% *6m* 63.0%	Conversion: 0% MI: 0% Stroke: 4% Sepsis: 4%	
Compassionate Clinical Use Studies											
North America											
Rodes-Cabau et al. 2011[87]	Prospective, single-center Enrollment: unknown	Edwards SAPIEN SAPIEN XT TF (38%) TA (62%)	TF N = 38 Age: 82 STS: 8.0% TA N = 63 Age: 78 STS: 8.6%	100%	*Baseline* TF/TA: 42 ± 17 * TF: 42 ± 12 TA: 42 ± 19 *Post-operative* TF/TA: 9 ± 3 * *TF/TA pooled	*Baseline* TF/TA: 0.62 ± 0.19 * TF: 0.62 ± 0.13 TA: 0.62 ± 0.21 *Post-operative* TF/TA: 1.65 ± 0.24 * *TF/TA pooled	*Baseline* TF/TA: 56 ± 13 * TF: 58 ± 2 TA: 54 ± 14 *6m* TF/TA: 58 ± 13 * *TF/TA pooled	*Baseline* ≥ III: TF/TA: 95 * TF: 89% TA: 97% *TF/TA pooled	*30d* All: 94% TF: 95% TA: 94%	Stroke TF: 6% TA: 3% Need for hemodialysis TF: 0% TA: 2% Need for pacemaker TF: 8% TA: 5%	Patients who died within 24 hours following the procedure (n=5) and those with major procedural complications were excluded.

Reference	Study design	Valve / Access	Number of patients / Baseline characteristics	Procedural success	Effectiveness Mean gradient (mmHg)	Mean aortic valve area (cm2)	Mean LVEF (%)	NYHA class	Survival	Major early complications	Length of stay/ Remarks
Rodés-Cabau et al. 2010[56] Multicenter Canadian Experience Program Canadian Compassionate Use	Prospective, multicenter Enrollment: 2005 - 2009	Edwards SAPIEN or SAPIEN XT TF TA	TF N = 168 Age: 83 STS: 9.0% TA N = 177 Age: 80 STS: 10.5%	TF: 90.5% TA: 96.1%	*Baseline* TF: 48 ± 18 TA: 44 ± 17 *Post-operative* 10 ± 4 * *TF/TA pooled	*Baseline* TF: 0.63 ± 0.16 TA: 0.63 ± 0.18 *Post-operative* 1.55 ± 0.41 * *TF/TA pooled	*Baseline* TF: 55 ± 14 TA: 56 ± 14	*Baseline* ≥III TF: 92.6% TA: 89.3%	*30d* TF: 90.5% TA: 88.7% *12m* TF: 75% TA: 78% *24m* TF: 65% TA: 64%	Conversion TF: 1.2% TA: 2.3% MI TF: 0.6% TA: 1.7% Pacemaker TF: 3.6% TA: 6.2% Stroke TF: 3.0% TA: 1.7% Sepsis TF: 3.0% TA: 2.8% Renal failure* TF: 1.8% TA: 3.4% * requiring hemodialysis	
Gurvitch et al. 2010[67] Canadian Compassionate Use	Prospective, single-center Enrollment: 2005-2006	Cribier-Edwards (70%) SAPIEN (30%) TF (78.6%) TA (21.4%)	N = 70 Age: 84.7 Log ES: 31.7% STS: 9.6%	100%	*Baseline* 45.0 *Post-operative* 10.0 *36m* 12.1	*Baseline* 0.6 ± 0.2 *Post-operative* 1.7 ± 0.4 *12m* 1.5 ± 0.3 *36m* 1.4 ± 0.3	*Baseline* ≤ 35%: 17.1%	*Baseline* ≥ III: 86% *12m* ≤ II: 93%	*12m* 81% *24m* 74% *36m* 61%	3y MI: 8.6% Cerebrovascular accident: 8.6% Reoperation: 1.4% Bleeding: 7.1% Endocarditis: 1.4% Pacemaker: 7.1% SVD: 0% Non-SVD: 0% Late valve embolization: 0% Valve thrombosis: 0%	This analysis only included patients with successful procedures and alive longer than 30 days

Reference	Study design	Valve / Access	Number of patients / Baseline characteristics	Procedural success	Effectiveness Mean gradient (mmHg)	Mean aortic valve area (cm2)	Mean LVEF (%)	NYHA class	Survival	Major early complications	Length of stay/ Remarks
Ye et al. 2010[72] Canadian Compassionate Use	Prospective single-center Enrollment: 2005-2009	Cribier Edwards or Edwards SAPIEN TA	N = 71 Age: 80.0 Log ES: 34.5% STS: 12.1%	100%	*Baseline* 43.6 ± 16.3 *30d* 10.1 ± 3.9	*Baseline* 0.6 ± 0.2 *30d* 1.4 ± 0.3	*Baseline* 55.5 ± 12.6 *24m* 61.2 ± 7.0	*Baseline* 3.3 ± 0.8 *24m* 1.8 ± 0.8	*30d* 83.1% *12m* 71.9% *24m* 66.3% *36m* 58%	PV leak (moderate): 5.2% Pacemaker: 8.5% Cerebrovascular accident: 1.4%	No SVD reported. Among patients who survived at least 30d, 24 and 36 month survivals were 79.8% and 69.9%, respectively
Bagur et al. 2009[104]	Prospective, multicenter Enrollment: 2005 - 2009	Cribier Edwards or Edwards SAPIEN TF (52%) TA (48%)	N = 213 Age: 82 Log ES: 29.3%	96%	*Baseline* 44 ± 17	*Baseline* 0.63 ± 0.16	*Baseline* 57 ± 14	*Baseline* ≥ III: 90%	*In-hospital* 90.2%	MI: 3% Stroke: 3% Renal failure: 1.4% * * requiring dialysis	Median LOS stay: 6 days
North America & Europe											
Clavel et al. 2010[63]	Prospective, multicenter Enrollment: 2005-2009	Cribier-Edwards or SAPIEN TF (53%) TA (47%)	TAVR N = 83 Age: 81 Log ES: 32% STS: 12% AVR N = 200 Age: 70 Log ES: 18% STS: 6%	NA	*Baseline* TAVR: 37 ± 14 AVR: 35 ± 14 *At Discharge* TAVR: 10 ± 5 AVR: 13 ± 5	*Baseline* TAVR: 0.64 ± 0.18 AVR: 0.72 ± 0.17 *At Discharge* TAVR: 1.65 ±0.55 AVR: 1.43 ± 0.42	*Baseline* TAVR: 34 ± 11 AVR: 34 ± 10 *12m* > 50 TAVR: 58% AVR: 20%	*Baseline* (median) TAVR: III AVR: III	*30d* TAVR: 81% AVR: 88%	Severe PPM TAVR: 16% AVR: 29% Moderate AR TAVR: 6% AVR: 0%	
Post-Marketing Studies											
Europe											

Reference	Study design	Valve / Access	Number of patients / Baseline characteristics	Procedural success	Effectiveness Mean gradient (mmHg)	Mean aortic valve area (cm2)	Mean LVEF (%)	NYHA class	Survival	Major early complications	Length of stay/ Remarks
Aktug et al. 2011[103]	Retrospective, single-center Enrollment: 2008-2010	Edwards SAPIEN TA (53%) CoreValve TF (47%)	N = 154 Age: 81 High or prohibitive risk	NA	NA	NA	*Baseline* ≥ 45: 73%	*Baseline* ≥ II: 84%	*30d* 88.3%	LBBB: 29% Pacemaker: 17%	LBBB was higher after CoreValve [38%] than after SAPIEN [16%] p=0.0006 Pacemaker implantation was higher after CoreValve [28%] than after SAPIEN [5%] p<0.001
Bleiziffer et al. 2011[106]	Retrospective, single-center Enrollment: 2007-2010	Edwards SAPIEN CoreValve TA	N = 143 Age 80.3 Log ES: 21% STS: 6.1%	NA	*Baseline* 47 ± 16	*Baseline* 0.67 ± 0.22	*Baseline* > 50%: 71% 31-50%: 24%	NA	*30d* 90.4% *6m* 77.5% *12m* 75.9%	Severe apical bleeding: 7% Any apical bleeding: 8% Re-exploration for post-op bleeding: 8% Apical pseudoaneurysm: 1% Secondary wound healing: 8% Stroke: 0.7% TIA: 1.4% MI: 2.8%	Institution employs TF first concept. TA only chosen when no TF access is available. Patient population is invariably sicker
Buz et al. 2011[62]	Prospective single-center Enrollment: 2008-2010	Edwards SAPIEN TA	N = 46 Age: 77.4 y Log ES: 45 STS: 23	96% primary valve 100% primary and secondary valve	*Baseline* 44.1 ± 15 *Post-operative* 5.8 ± 2.8	*Baseline* 0.68 ± 0.24 *Post-operative* 1.6 ± 0.43	*Baseline* 47 ± 15	*Baseline* ≥ IV: 17%	*30d* 100% *6m* 88% *12m* 85.2%	Pacemaker: 4.3% Cerebral emboli/infarcts 17.4% New cerebral ischemia 6.2%	

Reference	Study design	Valve / Access	Number of patients / Baseline characteristics	Procedural success	Effectiveness Mean gradient (mmHg)	Mean aortic valve area (cm2)	Mean LVEF (%)	NYHA class	Survival	Major early complications	Length of stay/ Remarks
Elhmidi et al. 2011[107]	Prospective, single-center Enrollment: 2007-2009	Edwards SAPIEN (26%) CoreValve (74%) TF TA SC	AKI+ N = 46 Age: 81.8 Log ES: 22.6% STS: 7.0% AKI- N = 188 Age: 80.7 Log ES: 21.1% STS: 5.9%	NA	*Baseline* AKI+: 43.1 ± 17.1 AKI-: 49.8 ± 16.9	*Baseline* AKI+: 0.65 ± 0.21 AKI-: 0.63 ± 0.18	NA	*Baseline* AKI+: 3.2 ± 0.3 AKI-: 3.0 ± 0.3	*In-hospital* All: 90.8% AKI+: 84.8% AKI-: 92.3% *6m* AKI+: 65% AKI-: 86%	Acute Kidney Injury (AKI): 19.6% RRT: 10.3% AR (I-III) AKI+: 64.4% AKI-: 66.1%	Mean overall LOS AKI+: 11.7 days AKI-: 8.7 days
Ewe et al. 2011[78] SOURCE Registry site	Retrospective, single-center Enrollment: initial 2.5 year experience	Edwards SAPIEN TF (43%) TA (57%)	N = 104 Age: 80.6 Log ES: 21.3% STS: 8.7%	92.5%	*Baseline* 41 ± 16 *Post-operative* 8 ± 3	*Baseline* 0.7 ± 0.2 *Post-operative* 2.0 ± 0.4	*Baseline* 53 ± 14 *Post-operative* 55 ± 13	*Baseline* ≥ III: 68%	*30d* 90.4% *6m* 87.2% *12m* 83.0%	Vascular complications: 10.6% Stroke: 3.8% Pacemaker: 3.8% Bleeding: 11.5% Major infection: 0%	Median overall LOS 6 days Early, midterm, clinical and echo outcomes were comparable in both approaches
Hernandez-Antolin et al. 2011[82]	Prospective, single-center Enrollment: 2007 - 2010	Cribier Edwards or SAPIEN (66%) CoreValve (34%) TF	N = 76 Age: 83 Log ES: 17.7% STS: 6.34%	90%	*Baseline* 48.6 ± 14.9 *Post-operative* 9.6 ± 5	*Baseline* 0.5 ± 0.2 *Post-operative* 1.7 ± 0.4	*Baseline* 62 ± 13	*Baseline* ≥ III: 76% *30d* ≥ III: 4%	Edwards THV *In-hospital* 84% *12m* 76% *24m* 76%	Stroke: 2.6% Vascular comp: 25% Pacemaker: 20% Dialysis: 3.9% Severe AR: 1.3%	
Jahangiri et al, 2011[108]	Prospective single-center Enrollment: 2008-2010	Edwards SAPIEN CoreValve TF TA SC	N = 63 Age: 82 y Log ES: 14 STS: 13	100%	*Baseline* 47 ± 17	*Baseline* 0.6 ± 0.1	NA	*Baseline* ≥ III: 81%	*30d* 100% *12m* 83%	TIA/CVA: 6.3% Vascular complication: 6.3% Pacemaker: 25% Hemofiltration: 6.3% Ventilation > 24 hr: 3.2% Wound infection: 1.6% Tracheostomy: 1.6%	Mean ICU stay: 0.5 days Mean hospital stay: 8.5 days

Reference	Study design	Valve / Access	Number of patients / Baseline characteristics	Procedural success	Effectiveness Mean gradient (mmHg)	Mean aortic valve area (cm2)	Mean LVEF (%)	NYHA class	Survival	Major early complications	Length of stay/ Remarks
Johansson et al. 2011[109]	Retrospective, single-center propensity matching analysis Enrollment: 2008 - 2009	Edwards SAPIEN TF TA	TF N = 10 Age:83 Log ES: 25.6% TA N = 30 Age: 80 Log ES: 23.5% AVR N = 40 Age: 81 Log ES 22.7%	TAVR: 92.5%	*Baseline* TF: 54 ± 24 TA: 45 ± 15	NA	*Baseline* < 30 TF: 20% TA: 10%	*Baseline* = IV TF: 10% TA: 37%	*30d* 95% *6m* 77% *12m* 77%	Major vascular comp TF: 30% TA: 0% Cerebrovascular ischemia TF: 20% TA: 3% Renal Failure TF: 10% TA: 10% Afib TF: 0% TA: 10% Pacemaker TF: 0% TA: 0%	A comparison of survival between TAVR and propensity score-matched AVR patients showed no significant difference in either the TA (p=0.73) or TF (p=0.59) groups Median ICU stay: TF: 34 hours TA: 40 hours Median LOS: TF: 13 days TA: 7 days
Lange et al. 2011[110]	Prospective, single-center Enrollment: 2007- 2010	Edwards SAPIEN CoreValve TART (69%) TA (31%)	TART N = 285 Age: 80.3 Log ES: 20.0% STS: 5.5% TA N = 127 Age: 80.2 Log ES: 20.5% STS: 5.8%	NA	*Baseline* TART: 48.2 ± 16.5 TA: 47.1 ± 15.9	*Baseline* TART: 0.68 ± 0.19 TA: 0.66 ± 0.22	*Baseline* 35-50%: TART: 17.9% TA: 23.6% < 35: TART: 19.6% TA: 5.5% ≤ 50: TART: 37.5% TA: 29.1	*Baseline* ≥ III TART: 96.1% TA: 99.2%	*30d* 90.9%* *6m* 78.9%* TART: 78.4% TA: 79.9% *12m* 77.4%* TART: 77.1% TA: 78.0% *TART/TA pooled	Vascular complications: 10.2% Pericardial tamponade: 2.9% Coronary ischemia: 1.9%	

Reference	Study design	Valve / Access	Number of patients / Baseline characteristics	Procedural success	Effectiveness Mean gradient (mmHg)	Mean aortic valve area (cm2)	Mean LVEF (%)	NYHA class	Survival	Major early complications	Length of stay/ Remarks
Mussardo et al, 2011[86]	Retrospective single-center Enrollment: SAPIEN: 2007-2010 SAPIEN XT: 2010	Edwards SAPIEN SAPIEN XT TF	SAPIEN n = 66 Age: 80.1 y Log ES: 26.5 STS: 7.2 SAPIEN XT n = 54 Age: 80.4 y Log ES: 22.9 STS: 7.1	SAPIEN 92.4% SAPIEN XT 96.3%	*Baseline* SAPIEN: 56.3 ± 18.2 SAPIEN XT: 54.8 ± 16.6 *30 d* SAPIEN: 9.9 ± 4.0 SAPIEN XT: 9.7 ± 3.6	NA	*Baseline* SAPIEN: 51.2% ± 11.4 SAPIEN XT: 53.4% ± 12.7	*Baseline* ≥ III: SAPIEN: 69.7% SAPIEN XT: 70.4%	*30d* SAPIEN: 100% SAPIEN XT: 96.3%	SAPIEN: TIA: 1.5% Stroke: 1.5% Bleeding: 25.8% AKI stage 3: 4.8% Vascular complications: 33.3% SAPIEN XT: TIA: 1.9% Cardiac death: 3.7% Stroke: 1.9% Bleeding: 18.5% Vascular complications: 11.1%	
Tamburino et al. 2011[88]	Prospective, single-center Enrollment: 2007 - 2010	Edwards SAPIEN XT CoreValve TF (98%) TA (2%)	N = 165 Age: 81 Log ES: 22.4% STS: 7.3%	95.7%	*Baseline* 57 ± 18 *30d* 10 ± 4	*Baseline* 0.6 ± 0.2 *30d* 1.5 ± 0.3	*Baseline* 51 ± 10	*Baseline* ≥ III: 61.1% 2.7 ± 0.7 *30d* 1.5 ± 0.6	*In-hospital* 99.4% *30d* 91.4% *12m* 81.6%	Myocardial infarction: 0% Stroke: 1.9% Conversion to open heart surgery: 0.6% Major bleedings: 2.5% MACCE: 5% Permanent PM: 23.5%	LES ≥ 20% : 48% LES < 20% : 52%
Taramasso et al. 2011[111]	Prospective single-center, Enrollment: 2007 – 2010	Edwards SAPIEN SAPIEN XT CoreValve 3rd Gen TF (80%) TA (11%) TAX (9%)	N = 177 Age: 79 TF Log ES: 26.7% STS: 20.6% TA Log ES: 33.6% STS: 28.3% TAX Log ES: 28.6% STS: 22.3%	98.8%	*Baseline* TF: 53.2 ± 17.2 TA: 42.5 ± 16 TAX: 47.5 ± 15	NA	*Baseline* TF: 50.7 ± 12.9 TA: 49.1 ± 12.7 TAX: 53.2 ± 10.6 *30d* TF: 53 ± 12 TA: 50 ± 10 TAX: 53 ± 10	*Baseline* ≥ III TF: 70% TA: 74% TAX: 60% *Follow-up* ≤ II TF: 93.4% TA: 91.7% TAX: 81.3%	*30d* TF: 98.6% TA: 87.5% TAX: 94.7% *6m* TF: 88.4% TA: 72.2% TAX: 67.4%	Vascular comp: TF: 17.2% Pacemaker: TF: 13.6% TA: 18.7% TAX: 5.2% Neurological event: TF: 2.2% TA: 0% TAX:5.2% Renal failure: TF: 4.3% TA: 25% TAX: 10.5%	Mean LOS TF: 9.3 days TA: 14.8 days TAX: 8.5 days

Reference	Study design	Valve / Access	Number of patients / Baseline characteristics	Procedural success	Effectiveness Mean gradient (mmHg)	Mean aortic valve area (cm2)	Mean LVEF (%)	NYHA class	Survival	Major early complications	Length of stay/ Remarks
Walther et al, 2011[94]	Retrospective single-center Enrollment: 2006-2010	Edwards SAPIEN TA	N = 299 Age: 82.1 y Log ES: 31 STS: 12	100%	*Postoperative* 8 *12m* 5 *24m* 5 *36m* 6	NA	*Postoperative* 56% *12m* 58% *24m* 58% *36m* 59%	*Baseline* ≥ III: 83.6%	*30d* 91% *12m* 73% *24m* 68% *36m* 58% *48m* 53%	Coronary ischemia: 3% 2nd valve: 5% Annulus perforation: 1%	
Witkowski et al, 2011[91]	Retrospective, single-center Enrollment: 2009-2010	Edwards SAPIEN CoreValve TF TA (37%) SC	N = 30 Age: 82.5 y Log ES: 29.2% TF/SC N = 19 Age: 82.0 y Log ES: 22.7% TA N = 11 Age: 83.2 y Log ES: 34.6%	96%	NA	*Baseline* TF/SC: 0.66 ± 0.11 TA: 0.7 ± 0.14	*Baseline* TF/SC: 53.7 ± 12.6 TA: 50.9 ± 13 *30d* TF/SC: 59.8 ± 8.8 TA: 59.4 ± 9.8	*Baseline* TF/SC: 3.21 ± 0.4 TA: 3.27 ± 0.44 *30d* TF/SC: 1.78 ± 0.55 TA: 1.6 ± 0.48	*30d* 93.4% TF/SC: 100% TA: 82%	Urgent cardiac surgery TA: 9% Periprocedural death TA: 9% Pacemaker TF/SC: 36.9% TA: 18% Pleural effusion TA: 18% Peripheral embolism TF/SC; 5.26% Gastrointestinal bleeding TF/SC: 5.26% Iatrogenic femoral artery stenosis TF/SC: 5.26% Inguinal haematoma TF/SC: 15.79% TA: 18% Thrombocytopenia TA: 9%	Mean overall LOS TF/SC: 11.8 days TA: 14.5 days

Reference	Study design	Valve / Access	Number of patients / Baseline characteristics	Procedural success	Effectiveness Mean gradient (mmHg)	Mean aortic valve area (cm2)	Mean LVEF (%)	NYHA class	Survival	Major early complications	Length of stay/ Remarks
Zhao et al. 2011[92]	Prospective, single-center Follow up: 1 and 6 weeks	NA	TAVR N = 20 Age: 79 Log ES: 19.3% STS: 17.1% AVR N = 30 Age: 62 Log ES: 4.0%	100%	*Baseline* TAVR: 51 ± 17 AVR: 54 ± 17 *1wk* TAVR: 14.7 ± 5.7 AVR: 16.8 ± 6.3	*Baseline* TAVR: 0.6 ± 0.1 AVR: 0.8 ± 0.3	*Baseline* TAVR: 54 ± 8.3 AVR: 65 ± 6.7 *1wk* TAVR: 57 ± 7.2 AVR: 65 ± 7.4 *6wks* TAVR: 60 ± 5.3	*Baseline* ≥ III: TAVR: 100% 3.3 ± 0.5 AVR: 40% *6wks* TAVR: 1.9 ± 0.4	*6wks* 100%	NA	
Attias et al. 2010[61]	Prospective, single-center Enrollment: 2006-2009	Edwards SAPIEN (87%) CoreValve (13%) TF	N = 83 Age: 81 Log ES: 26% STS: 15%	94%	*Baseline* 52 ± 16 *30d* 11 ± 4	*Baseline* 0.69 ± 0.18 *30d* 1.7 ± 0.4	*Baseline* 52 ± 15	*Baseline* ≥ III: 97% *Last follow-up* ≤ II: 82%	*30d* 93% *12m* 78% *24m* 71%	Paravalvular AR (Grade III/IV): 4% Major vascular comp: 12% Stroke: 5% Tamponade: 2% Heart block: 8% SVD: 0%	Median LOS stay: 12 days
Conradi et al. 2010[64]	Retrospective, single-center Enrollment: 2008-2010	Edwards SAPIEN (89%) CoreValve (11%) TF TA	N = 28 Age: 80.1 Log ES: 26.8% STS: 9.3%	96.4%	*Baseline* 40.2 ± 16.8 *Post-operative* 9.3 ± 4.2	*Baseline* NA *Post-operative* 1.74 ± 0.47	*Baseline* 45.6 ± 11.1	*Baseline* 3.0 ± 0.5	*30d* 92.9%	AR Mild-to-moderate: 54% Severe: 3.5% Renal failure: 7% Pacemaker: 7% Non-severe bleeding complication: 3.5%	Mean ICU stay: 3.1 days Mean LOS: 12.2 days In all 28 patients PCI was performed either as a staged approach up to 4 weeks prior to TAVR (n=21) or in a single-stage procedure (n=7)

Reference	Study design	Valve / Access	Number of patients / Baseline characteristics	Procedural success	Effectiveness Mean gradient (mmHg)	Mean aortic valve area (cm2)	Mean LVEF (%)	NYHA class	Survival	Major early complications	Length of stay/ Remarks
Covello et al. 2010[65]	Prospective, single-center Enrollment: 2007-2009	Edwards SAPIEN CoreValve TF SC	N = 69 Age: 78.8 Log ES: 26.5%	100%	*Baseline* 53.7 ± 15.5 *Post-operative* 10.7 ± 3.7	NA	*Baseline* 51.2 ± 12.1 *Post-operative* 49.9 ± 12.1	≥ III: 67%	*30d* 100% *6m* 86%	AR Mild-to-moderate: 33% Severe: 4% MI: 0% Renal failure 10% Pacemaker: CoreValve: 6% SAPIEN: 4% Stroke: 1% Vascular complications: 23%	Mean ICU stay 20.1 hours Mean overall LOS: 9.0 days
Drews et al. 2010[75]	Retrospective, single-center Enrollment: 2008-2009	Edwards SAPIEN TA	*Group A* (no previous heart operation) N = 158 Age: 80 Log ES: 37% STS: 21% *Group B* (previous heart operation) N = 40 Age: 75 Log ES: 53% STS: 29%	Group A: 99.5% Group B: 100% (technical success)	*Baseline* A: 49 ± 13.7 B: 42 ± 19.6 *Post-operative* A: 5 ± 2.2 B: 6 ± 4.7	*Baseline* A: 0.65 ± 0.16 B: 0.7 ± 0.3	*Baseline* A: 51 ± 13.8 B: 43 ± 14.6	*Baseline* NA *12m* A: 2 ± 0.8 B: 2 ± 0.7	*30d* A: 93.1% B: 95.0% *6m* A: 79% B: 82% *12m* A: 77% B: 74% *24m* A: 68% B: 52%	Pacemaker: Group A: 8% Group B: 0% Central AV insufficiency Group A: 15% Group B: 5% Paravalvular AV insufficiency Group A: 29% Group B: 40%	Mean ICU stay Group A: 4.1 days Group B: 4.6 days Mean overall LOS Group A: 29.6 days Group B: 30 days
Dworakowski et al. 2010[76] SOURCE Registry site	Prospective, single-center Enrollment: 2007-2009	Edwards SAPIEN TF (44%) TA (56%)	N = 151 Age:82.6 Log ES:21.6%	98%	*Baseline* 48.8 ± 1.4 *Discharge* 5.8 ± 0.4	*Baseline* 0.62 ± 0.16	NA	*Baseline* ≥ III: 70% *30d* ≤ II: 85%	*30d* 90.1% *12m* TF: 83.6% TA: 70.2%	Stroke: 6% Pacemaker: 5.3% Renal failure: 9.3% Major vascular comp: 8.6% Severe AR: 0.7%	Mean LOS stay TF: 11 days TA: 19 days

Reference	Study design	Valve / Access	Number of patients / Baseline characteristics	Procedural success	Effectiveness Mean gradient (mmHg)	Mean aortic valve area (cm2)	Mean LVEF (%)	NYHA class	Survival	Major early complications	Length of stay/ Remarks
Ewe et al. 2010[77] SOURCE Registry site	Retrospective, multi-center Enrollment: unknown	Edwards SAPIEN TF TA	N = 147 EF≥50%: n=97 EF<50%: n=50 Age: 80 Log ES: 21.8%	96%	*Baseline* EF≥50%: 52 ± 17 EF<50%: 40 ± 15 *Post-operative* EF≥50%: 11 ± 5 EF<50%: 10 ± 4	*Baseline* EF≥50%: 0.66 ± 0.16 EF<50%: 0.68 ± 0.17 *Post-operative* EF≥50%: 2.09 ± 0.42 EF<50%: 2.08 ± 0.49	*Baseline* EF≥50%: 61 ± 7 EF<50%: 37 ± 8 *Post-operative* EF≥50%: 59 ± 11 EF<50%: 46 ± 11	*Baseline* ≥ III: EF≥50%: 67% EF<50%: 90%	*30d* Overall: 93% EF≥50%: 95% EF<50%: 90% *6m* EF≥50%: 90% EF<50%: 86% *12m* EF≥50%: 86% EF<50%: 82%	Vascular comp: 7% MI: 1% Severe AR: 1% HF: 3% Stroke: 3% Pacemaker: 5 %	
Ferrari et al. 2010[79]	Retrospective, single-center Enrollment: 2008-2009	Edwards SAPIEN TA	N = 30 Age: 80.1 Log ES:32.2%	96.7%	*Baseline* 60.3 ± 20.9 *Post-operative* 7.7 ± 4.8	*Baseline* 0.7 ± 0.16	*Baseline* 52.6 ± 12.8 *Post-operative* 55.7 ± 10.5	NA	*30d* 90%	Renal failure: 0% MI: 0% Exploration for bleeding: 6.6% Stroke: 3.3% PV leak (moderate): 10%	Mean ICU stay: 2.4 day Mean LOS: 15.1 days
Godino et al. 2010[81]	Retrospective, Single-center Enrollment: 2007 - 2010	Edwards SAPIEN (58%) CoreValve (42%) TF (78%) TA (11%) TAX (11%)	TF N = 107 Age:79.7 Log ES: 26.6% STS: 7% TA N = 15 Age: 78.8 Log ES: 32.2% STS: 8.3% TAX N = 15 Age: 78.7 Log ES: 28.6 STS: 6.9%	TF: 93.5% TA: 87% TAX: 93%	*Baseline* TF: 54 ± 17.2 TA: 44.7 ± 18 TAX: 47.7 ± 14.9 *6m* TF: 11 ± 9 TA: 19 ± 8 TAX: 9 ± 3	NA	*Baseline* TF: 51 ± 12.9 TA: 50 ± 12.5 TAX: 53 ± 11 *6m* TF: 53 ± 9 TA: 56 ± 4 TAX: 60 ± 3	*Baseline* ≥ III TF: 70% TA: 73% TAX: 60%	*30d* TF: 99% TA: 87% TAX: 100% *6m* TF: 88% TA: 73% TAX: 87%	AR ≥ grade 3 TF: 6.5% TA: 13% TAX: 6.6% Major vascular comp TF: 20.6% TA: 0% TAX: 6.6% Stroke TF: 0.9% TA: 0% TAX: 0% Renal failure TF: 4.7% TA: 27% TAX: 13% Pacemaker TF: 17.8% TA: 20% TAX: 13%	Mean LOS: TF: 9.5 days TA: 15.8 days TAX: 8.7 days

Reference	Study design	Valve / Access	Number of patients / Baseline characteristics	Procedural success	Effectiveness Mean gradient (mmHg)	Mean aortic valve area (cm2)	Mean LVEF (%)	NYHA class	Survival	Major early complications	Length of stay/ Remarks
Kempfert et al. 2010[85]	Retrospective, single-center Enrollment: 2006 - 2009	Edwards SAPIEN TA	N = 29 Age: 79 Log ES: 37.7% STS: 12.8%	100%	*Baseline* 44.4 ± 18.6 *Post-operative* 9.3 ± 3.9		*Baseline* 54.5 ± 14.1 *Post-operative* 56.9 ± 10.6	*Baseline* 3 ± 0.5	*30d* 82.8%	Paravalular leak Mild: 31% Moderate: 3.4% Severe: 0% Renal Failure: 31% Stroke: 3.4% Pacemaker: 17.2%	All 29 patients were identified as having true porcelain aorta. Median ICU stay: 1 day
Pasic et al. 2010[57]	Retrospective single-center Enrollment: 2008 - 2009	Edwards SAPIEN TA	N = 175 Age: 79.8 Log ES: 38.3% STS: 23.5%	100%	*Baseline* 46.5 ± 13.9 *Post-operative* 6.28 ± 2.94	*Baseline* 0.57 ± 0.22 *Post-operative* 1.88 ± 0.51	*Baseline* 52 ± 18	*Baseline* ≥ III: 98%	*30d* 94.9% *6m* 85.5% *12m* 82.6%	Bleeding: 2% Surgical revision: 1% Pacemaker: 5.7% Aortic dissection: 0% Valve dislocation: 0% SVD: 0% MI: 0.6% Wound infection: 1.1% Thrombosis: 0.6% Abdominal comp: 1.7% Neurological deficit: 0.6% Severe central valvular regurgitation: 0.6% Endocarditis: 0.6%	
Tchetche et al. 2010[89]	Prospective, multicenter Enrollment: 2007-2009	Edwards SAPIEN (53%) CoreValve (47%) TF	N = 45 Age: 81.8 Log ES: 25.2%	97.8%	*Baseline* 41.9 ± 14 *30d* 9.50 ± 3.28	*30d* 0.92 ± 0.23* * EOA	*Baseline* 45.6 ± 16.4 *30d* 46.5 ± 17.7	*Baseline* ≥ III: 95.6% *30d* ≤ II: 88.4% 2.07 ± 0.4	*30d* 97.5%	Pacemaker: 15.6% MI: 11.1% Stroke: 0% Renal failure: 22.8%	Mean LOS: 12.8 days

Reference	Study design	Valve / Access	Number of patients / Baseline characteristics	Procedural success	Effectiveness Mean gradient (mmHg)	Mean aortic valve area (cm2)	Mean LVEF (%)	NYHA class	Survival	Major early complications	Length of stay/ Remarks
Walther et al. 2010[112] SOURCE Registry site	Retrospective, single center, propensity matched analysis Enrollment (TA): 2006 - 2008	Edwards SAPIEN TA vs. Propensity matched HRAVR patients	TA N = 100 Age: 82.7 Log ES: 29% STS: 15.2% HRAVR N = 100 Age: 82.4 Log ES: 30% STS: NA	TA: 97%	NA	NA	*Baseline* TA: 54 ± 15 HRAVR: 56.3 ± 18 *6m* TA: 59 ± 12 HRAVR: NA *12m* TA: 58 ± 12 HRAVR: NA	*Baseline* TA: 3.2 ± 0.4 HRAVR: 3.1 ± 0.6 *3-6m* TA: 2.3% HRAVR: NA *12m* TA: 2.4% HRAVR: NA	*30d* TA: 90% HRAVR: 85% *6m* TA: 75% HRAVR: 70% *12m* TA: 73% HRAVR: 69%	Conversion TA: 3% Pacemaker TA: 9% Stroke TA: 0% HRAVR: 2%	Surgical control patients all underwent isolated AVR
Aregger et al. 2009[60]	Retrospective, single-center Enrollment: 2007-2008	Edwards SAPIEN CoreValve TF (79%) TA (21%)	N = 58 Age: 83 Log ES: 27%	97%	*Baseline* 51.2 ± 17 *Post-operative* 9.4 ± 4.9	NA	*Baseline* 49 ± 15	*Baseline* ≥ III: 79%	*30d* 93.1%	Renal Failure: 7.4%	Median LOS stay: 11 days
Bleiziffer et al. 2009[105]	Retrospective, single-center Enrollment: 2007-2009	Edwards SAPIEN CoreValve TF (75%) TA (25%)	TF N = 153 Age: 81.4 Log ES: 22.1% STS: 6.5% TA N = 50 Age: 81.5 Log ES: 22.0% STS: 6.3%	98.5%	NA	NA	*Baseline* < 50% TF: 42% TA: 34%	*Baseline* TF: 3.1 ± 0.3 TA: 3.1 ± 0.2 *Post-operative* TF: 1.7 ± 0.6 TA: 1.6 ± 0.6	*30d* TF: 88.8% TA: 91.7% *6m* TF: 80.1% TA: 73.4%	Neurologic events TF: 7% Femoral vessel complication TF: 16% Bleeding TA: 10% LV aneurysm TA: 2%	
Fusari et al. 2009[80]	Retrospective, single-center Enrollment: 2007-2008	Edwards SAPIEN TF TA	N = 22 Age: 80 Log ES: 30.28%	95.5%	*Baseline* 54.4 ± 17.1 *Post-operative* 12.4 ± 4.1	*Baseline* 0.65 ± 0.14 *Post-operative* 2.2 ± 0.4	*Baseline* 51.8 ± 12.5 *Post-operative* 52.8 ± 11.3	*Baseline* median III	*30d* 95.5	Stroke: 0% MI: 0% Renal failure: 33% Vascular complication: 13.6%	Mean overall LOS: 9 days

Reference	Study design	Valve / Access	Number of patients / Baseline characteristics	Procedural success	Effectiveness Mean gradient (mmHg)	Mean aortic valve area (cm2)	Mean LVEF (%)	NYHA class	Survival	Major early complications	Length of stay/ Remarks
Himbert et al. 2009[83]	Prospective, single-center Enrollment: 2006 - 2008	Edwards SAPIEN TF TA	TF N = 51 Age: 82 Log ES: 25% STS: 15% TA N = 24 Age: 82 Log ES: 28% STS: 18%	TF: 90% TA: 100%	*Baseline* TF: 54 ± 15 TA: 48 ± 14 *Post-operative* TF: 11 ± 4 TA: 9 ± 4	*Baseline* TF: 0.63 ± 0.16 TA: 0.65 ± 0.17 *Post-operative* TF: 1.70 ± 0.37 TA: 1.80 ± 0.48	*Baseline* TF: 52 ± 16 TA: 48 ± 13	*Baseline* ≥ III: 94% TF: 3.4 TA: 3.3	*In-hospital* TF: 92% TA: 84% *12m* TF: 81% TA: 74%	Conversion TF: 0% TA: 0% Pacemaker TF: 6% TA: 4% Stroke TF: 6% TA: 0%	Median ICU stay: TF: 2.5 days TA: 5 days Median total LOS TF: 13 days TA: 12 days
Kahlert et al. 2009[84]	Retrospective, single-center Enrollment: 2006 – unknown	Edwards SAPIEN (68%) CoreValve (32%) TF	N = 60 Age: 79.6 Log ES: 21.64%	98%	*Baseline* 51.6 ± 17.8 *Post-operative* 13.1 ± 6.4	*Baseline* 0.60 ± 0.16 *Post-operative* 1.50 ± 0.34	*Baseline* 48.3 ± 12.7	*Baseline* median III *Post-operative* median II	*30d* 88%	Stroke: 0% Access complications: 32% Pacemaker: 22%	
Zierer et al. 2009[93]	Prospective, single-center Enrollment: 2006 – 2007	Cribier Edwards TA (41%) Minimally invasive AVR (59%)	TA N = 21 Age: 85 Log ES: 38% Min-Inv-AVR N = 30 Age: 82 Log ES: 35%	100%	*12m* TA: 9.6 ± 3.7 MI-AVR: 7.3 ± 3.7	*12m* TA: 1.5 ± 0.8 MI-AVR: 1.7 ± 0.5	*Baseline* <30% TA: 24% MI-AVR: 20%	*Baseline* TA: 3.4 ± 0.4 MI-AVR: 3.2 ± 0.2	*30d* TA: 86% MI-AVR: 90% *12m* TA: 76% MI-AVR: 83%	Re-exploration: 8% Stroke: 0% arrhythmia: 19% transient hemofiltration: 12% AI mild-to-moderate: 15%	Mean ICU stay TA: 1 day MI-AVR: 3.2 days Mean total LOS TA: 5 days MI-AVR: 12 days
Randomized Trials											
North America & Europe											

Reference	Study design	Valve / Access	Number of patients / Baseline characteristics	Procedural success	Effectiveness Mean gradient (mmHg)	Mean aortic valve area (cm2)	Mean LVEF (%)	NYHA class	Survival	Major early complications	Length of stay/ Remarks
Smith et al. 2011[53] US PARTNER Trial (Cohort A)	Prospective, multicenter, RCT Enrollment: 2007-2009	Edwards SAPIEN TF (70%) TA (30%) AVR	TAVR N = 348 Age: 83.6 Log ES: 29.3% STS: 11.8% AVR N = 351 Age: 84.5 Log ES: 29.2% STS: 11.7%	NA	*Baseline* TAVR: 42.7 ± 14.6 AVR: 43.5 ± 14.3 *30d* TAVR: 9.9 ± 4.8 AVR: 10.8 ± 5.0 *12m* TAVR: 10.2 ± 4.3 AVR: 11.5 ± 5.4	*Baseline* TAVR: 0.7 ± 0.2 AVR: 0.6 ± 0.2 *30d* TAVR: 1.7 ± 0.5 AVR: 1.5 ± 0.4 *12m* TAVR: 1.6 ± 0.5 AVR: 1.4 ± 0.5	*Baseline* TAVR: 52.5 ± 13.5 AVR: 53.3 ± 12.8 *30d* TAVR: 56 ± 11 AVR: 56 ± 11 *12m* TAVR: 57 ± 11 AVR: 57 ± 10	*Baseline* ≥III TAVR: 94.3% AVR: 94% *30d* More TAVR patients had a reduction in symptoms – NYHA ≤ II (p<0.001)	*30d* TAVR: 96.6% AVR: 93.5% *12m* TAVR: 75.8% AVR: 72.3%	Stroke (major) TAVR: 3.8% AVR: 2.1% MI TAVR: 0 AVR: 0.6% Vascular comp (major) TAVR: 11.0% AVR: 3.2% RRT TAVR: 2.9% AVR: 3.0% Major bleeding TAVR: 9.3% AVR: 19.5% A-fib TAVR: 8.6% AVR: 16.0% Pacemaker TAVR: 3.8% AVR: 3.6%	All patients considered high-risk operable Median ICU stay TAVR: 3 days AVR: 5 days Median LOS TAVR: 8 days AVR: 12 days

Reference	Study design	Valve / Access	Number of patients / Baseline characteristics	Procedural success	Effectiveness Mean gradient (mmHg)	Mean aortic valve area (cm2)	Mean LVEF (%)	NYHA class	Survival	Major early complications	Length of stay/ Remarks
Leon et al. 2010[3] US PARTNER Trial (Cohort B)	Prospective, multicenter, RCT Enrollment: 2007-2009	Edwards SAPIEN TF vs. Standard therapy (ST)	TF N = 179 Age : 83.1 Log ES : 26.4% STS: 11.2% ST N = 179 Age: 83.2 Log ES: 30.4% STS: 12.1%	NA	*Baseline* TF: 44.5 ± 15.7 ST: 43.0 ± 15.3 *1m* TF: 11.4 ± 7.0 ST: 33.1 ± 12.6 *12m* TF: 13.2 ± 11.2 ST: 44.3 ± 16.1	*Baseline* TF: 0.6 ± 0.2 ST: 0.6 ± 0.2 *1m* TF: 1.5 ± 0.4 ST: 0.8 ± 0.2 *12m* TF: 1.6 ± 0.5 ST: 0.7 ± 0.3	*Baseline* TF: 53.9 ± 13.1 ST: 51.1 ± 14.3 *1m* TF: 57.9 ± 10.1 ST: 51.7 ± 13.9 *12m* TF: 57.2 ± 10.6 ST: 56.9 ± 10.3	*Baseline* ≥ III TF: 92.2% ST: 93.9% *12m* ≤ II TF: 74.8% ST: 42.0%	*30d* TF: 95.0% ST: 97.2% *12m* TF: 69.3% ST: 49.3%	Stroke (major): TF: 5.0% ST: 1.1% MI TF: 0% ST: 0% Major vascular comp TF: 16.2% ST: 1.1% RRT TF: 1.1% ST: 1.7% Major bleeding TF: 16.8% ST: 3.9% New A-fib TF:0.6% ST: 1.1% Pacemaker TF: 3.4% ST: 5.0%	All patients were not suitable candidates for surgery (i.e., "inoperable") 83.8% of ST patients received BAV
Registries											
Europe											
Thomas et al, 2011[54] SOURCE Registry Cohort 1	Prospective, multicenter European registry Enrollment: 2008-2009	Edwards SAPIEN TF TA	TF n = 463 Age: 81.7 y Log ES: 25.8 TA n = 575 Age: 80.7 y Log ES: 29.1	NA	NA	NA	NA	*Baseline* = IV TF: 14.7% TA: 13.6%	*12m* TF/TA: 76.1% TF: 81.1% TA: 72.1%	NA	

Reference	Study design	Valve / Access	Number of patients / Baseline characteristics	Procedural success	Effectiveness Mean gradient (mmHg)	Mean aortic valve area (cm2)	Mean LVEF (%)	NYHA class	Survival	Major early complications	Length of stay/ Remarks
Thomas et al. 2010[55] SOURCE Registry Cohort 1	Prospective, multicenter European registry Enrollment: 2007 - 2009	Edwards SAPIEN TF (45%) TA (55%)	TF N = 463 Age: 81.7 Log ES: 25.7% TA N = 575 Age: 80.7 Log ES: 29.1%	93.8%	NA	NA	NA	NA	*30d* 91.5%	Stroke: 2.5% Renal failure: 4.3% Pacemaker: 7.0% Major vascular comp: 7.0% AR>grade 2+ 1.9% Conversion: 2.7% Valve embolization: 0.3% Coronary obstruction 0.6% Transfusion: 9.3%	

National TAVR registries

Reference	Study design	Valve / Access	Number of patients / Baseline characteristics	Procedural success	Effectiveness				Survival	Major early (30d) complications	Length of stay/ Remarks
					Mean gradient (mmHg)	Mean aortic valve area (cm2)	Mean LVEF (%)	NYHA class			
Eltchaninoff et al. 2010[66] FRANCE Registry	Prospective, multicenter national registry Enrollment: 2009-2009	Edwards SAPIEN (68%) CoreValve (32%) TF (66.0%) TA (29.1%) SC (4.9%)	N = 244 Age: 82.3 Log ES: 25.6% STS: 18.9%	98.3%	*Baseline* 46.2 ± 15.6 *Post-operative* 10.7 ± 5.0	*Baseline* 0.68 ± 0.16 *Post-operative* 1.74 ± 0.47	*Baseline* 51 ± 14	*Baseline* ≥ 3: 74.5%	*30d* 87.3	Stroke: 3.6% Pacemaker: 11.8% Vascular complications: 7.3% Renal Failure: 1.6% Paravalvular leak Grade II: 9% Grade IV: 0.5%	New Pacemaker rates SAPIEN: TF: 5.3% TA: 5.6% CoreValve: TF: 25.7% TS: 25%
Bosmans et al, 2011[101] Belgian Registry	Prospective, multicenter national registry Enrollment: Until 2010	Edwards SAPIEN (57%) CoreValve (43%) TF (71%) TA (27%) SC (2%)	N = 328 Age: 83 y Log ES: 28%	97%	*Baseline* 49 ± 16	*Baseline* 0.61 ± 0.15	*Baseline* 55 ± 14	*Baseline* ≥ III: 79%	*30d* Edwards: TF 94% TA 86% CoreValve 91% *6m* Edwards: TF 91% TA 71% CoreValve 82% *12m* Edwards: TF 82% TA 63% CoreValve 79%	Edwards: Pacemaker 5% Renal failure 6% Stroke 5% TIA 1% CoreValve: Pacemaker 22% Renal failure 7% Stroke 4% TIA 1%	
D'Onofrio et al. 2011[102] Italy TA Registry	Prospective, multicenter Enrollment: 2008-2010	Edwards SAPIEN TA	N = 504 Age: 81.2 Log ES: 24% STS: 11%	99%	*Baseline* 47.4 ± 15.4 *Post-operative* 8.7 ± 4.1	*Baseline* 0.53 ± 0.18	*Baseline* 52.4 ± 13.6	*Baseline* ≥ III: 83%	*30d* 92% *12m* 81% *24m* 72%	Severe intraoperative complications: 4.8% Dialysis: 6.1% Trivial AR: 29.9% Mild AR: 8.6% Pacemaker: 5.3% Major stroke: 3% MI: 1.6%	Median ICU LOS: 2 days Mean hospital LOS: 9 days

Reference	Study design	Valve / Access	Number of patients / Baseline characteristics	Procedural success	Effectiveness Mean gradient (mmHg)	Mean aortic valve area (cm2)	Mean LVEF (%)	NYHA class	Survival	Major early (30d) complications	Length of stay/ Remarks
Moat et al. 2011 UK TAVR Registry	Prospective, multicenter Enrollment: 2007-2009	Edwards SAPIEN (48%) CoreValve (52%) TF (69%) Other (31%)	N = 870 Age: 81.9 Log ES: 18.5%	97.2%	NA	NA	*Baseline* ≥ 50%: 64% 30-49%: 27% <30%: 9%	*Baseline* ≥ III: 77%	*30d* 92.9% *12m* 78.6% *24m* 73.7%	Stroke: 4.1% MI: 1.3% AR (grade ≥ 1): 61% AR (grade ≥ 2): 14% Major vascular complications: 6.3% Pacemaker SAPIEN: 7.4% CoreValve: 24.4%	
Zahn et al. 2011[73] German TAVR Registry	Prospective, multicenter Enrollment: 2009 - 2009	Edwards SAPIEN (15.6%) CoreValve (84.4)	n = 697 Age: 81.4 Log ES: 20.5%	98.4% (technical success)	*Baseline* 48.7 ± 17.2 *Post-operative* 5.4 ± 6.2	*Baseline* 0.6 ± 0.2	*Baseline* <30: 14.6% 52.1 ± 15.0	*Baseline* ≥ III: 88.2%	*Post-operative* 91.8% *30d* 87.6%	AR: 72.4% Pericardial tamponade: 1.8% Stroke: 2.8%	Median ICU stay: 2 days Mean LOS: 17.2 days

Table 19: Other TAVR Studies Not Reported

Reference	Valve type	Reason for exclusion
Abdel-Wahab et al. 2011[138]	Edwards SAPIEN or CoreValve	Subpopulation of study cohort described by Zahn et al. 2011[73]
Al Ali et al. 2008[139]	Cribier Edwards & SAPIEN	Unclear whether 30-day mortality reported for entire cohort or just subset with valve malposition (n = 9)
Avanzas et al. 2010[140]	CoreValve	Exclusively CoreValve
Baan et al. 2010[141]	CoreValve	Exclusively CoreValve
Bagur et al. 2011[142-144]	Edwards SAPIEN	Subpopulation of study cohort described by Rodés-Cabau et al. 2010[56]; no survival results reported
Berry et al. 2007[145]	CoreValve	Small TAVR sample (n=11)
Bleiziffer et al. 2009[146,147]	Edwards SAPIEN or CoreValve	Subpopulation of study cohort described by Bleiziffer et al. 2009[105]
Buellesfeld et al. 2010[148]	CoreValve	Exclusively CoreValve
Buellesfeld et al. 2011[149]	CoreValve	Exclusively CoreValve
Chodor et al. 2010[150]	Edwards SAPIEN	Small TAVR sample (n=12)
De Carlo et al. 2010[151]	CoreValve	Exclusively CoreValve
De Robertis et al. 2009[152]	CoreValve	Small TAVR sample (n=7)
Descoutures et al. 2008[153]	Edwards SAPIEN	Small TAVR sample (n=12)
Detaint et al. 2009[154]	Edwards SAPIEN	No survival results reported
Dewey et al. 2008[14]	Edwards SAPIEN	Subpopulation of study cohort described by Leon et al. 2010[3] & Smith et al. 2011[53]
Dewey et al. 2010[155]	Edwards SAPIEN	Subpopulation of study cohort described by Leon et al. 2010[3] & Smith et al. 2011[53]
Di Bello et al. 2011[156]	CoreValve	No survival results reported
ElBardissi et al. 2011[157]	NA	Study does not include TAVR patients
Falk et al. 2010[158]	CoreValve	Exclusively CoreValve
Giannini et al. 2011[159]	CoreValve	No survival results reported
Gotzmann et al. 2010[97,160]	CoreValve	Exclusively CoreValve
Gotzmann et al. 2011[161]	CoreValve	Exclusively CoreValve
Grube et al. 2006[162]	CoreValve	Exclusively CoreValve
Grube et al. 2007[163]	CoreValve	Exclusively CoreValve
Guinot et al. 2010[164]	Edwards SAPIEN or CoreValve	Subpopulation of study cohort described by Himbert et al. 2009[83]
Gutierrez et al. 2009[165]	Edwards SAPIEN	Subpopulation of study cohort described by Rodés-Cabau et al. 2010[56]
Jilaihawi et al. 2009[166]	CoreValve	Exclusively CoreValve
Kapadia et al. 2009[15]	Cribier Edwares	Subpopulation of study cohort described by Kodali et al 2011[68]

Reference	Valve type	Reason for exclusion
Koos et al. 2011[167,168]	Edwards SAPIEN CoreValve	No survival results reported
Lichtenstein et al. 2006[169]	Cribier Edwards	Subpopulation of study cohort described by Rodés-Cabau et al. 2010[56]
Lopez-Otero et al. 2011[170]	CoreValve	Exclusively CoreValve
Marcheix et al. 2007[171]	CoreValve	Small TAVR sample (n=10)
Modine et al. 2010[172]	CoreValve	Exclusively CoreValve
Nielsen et al. 2011[173]	Edwards SAPIEN	Subpopulation of study cohort described by Thomas et al. 2010[55]
Nuis et al. 2011[174,175]	CoreValve	Exclusively CoreValve
Osten et al. 2009[176]	Edwards SAPIEN	Subpopulation of study cohort described by Rodés-Cabau et al. 2010[56]
Otten et al. 2008[17]	CoreValve	Exclusively CoreValve
Pasic et al. 2010[177]	Edwards SAPIEN	Subpopulation of study cohort described by Pasic et al. 2010[57]
Petronio et al. 2010[178]	CoreValve	Exclusively CoreValve
Piazza et al. 2008[179]	CoreValve	Exclusively CoreValve
Piazza et al. 2009[180]	CoreValve	Exclusively CoreValve
Piazza et al. 2010[181-183]	CoreValve	Exclusively CoreValve
Podolecka et al. 2011[184]	Edwards SAPIEN CoreValve	No survival results reported
Rajani et al. 2010[185]	CoreValve	Exclusively CoreValve
Ree et al. 2008[186]	Edwards SAPIEN	Subpopulation of study cohort described by Rodés-Cabau et al. 2010[56]
Rodes-Cabau et al. 2008[187]	Edwards SAPIEN	Subpopulation of study cohort described by Rodés-Cabau et al. 2010[56]
Spargias et al. 2008[188]	Edwards SAPIEN	Small TAVR sample (n=12)
Tamburino et al. 2009[189]	CoreValve	Exclusively CoreValve
Tamburino et al. 2011[190]	CoreValve	Exclusively CoreValve
Treede et al. 2010[191]	Direct Flow	Exclusively Direct Flow
Tzikas et al. 2011[192,193]	CoreValve	Exclusively CoreValve
Van Linden et al. 2011[194]	Edwards SAPIEN	Subpopulation of study cohort described by Walther et al. 2011[94]
Van Linden et al. 2011[195]	Edwards SAPIEN	Subpopulation of study cohort described by Walther et al. 2011[94]
Van Mieghem et al. 2010[196]	CoreValve	No survival results reported
Vavuranakis et al. 2010[197]	CoreValve	Exclusively CoreValve
Walther et al. 2008[127]	Edwards SAPIEN	Subpopulation of study cohort described by Walther et al. 2011

Reference	Valve type	Reason for exclusion
Walther et al. 2009[198]	Edwards SAPIEN	Subpopulation of study cohort described by Walther et al. 2011
Webb et al. 2006[199]	Cribier Edwards	Subpopulation of study cohort described by Rodés-Cabau et al. 2010[56]
Webb et al. 2007[200]	Cribier Edwards	Subpopulation of study cohort described by Rodés-Cabau et al. 2010[56]
Webb et al. 2007[201]	Cribier Edwards	Subpopulation of study cohort described by Rodés-Cabau et al. 2010[56]
Webb et al. 2009[202]	Edwards SAPIEN	Subpopulation of study cohort described by Rodés-Cabau et al. 2010[56]
Wendler et al. 2010[58]	Edwards SAPIEN	Subpopulation of study cohort described by Thomas et al. 2010[55]
Wendler et al. 2010[203]	Edwards SAPIEN	Subpopulation of study cohort described by Thomas et al. 2010[55]
Ye et al. 2007[204]	Cribier Edwards	Subpopulation of study cohort described by Rodés-Cabau et al. 2010[56]
Ye et al. 2009[205]	Edwards SAPIEN	Subpopulation of study cohort described by Rodés-Cabau et al. 2010[56]
Zahn R et al. 2011[206]	CoreValve	No survival results reported
Zierer et al. 2008[207]	Cribier Edwards	Subpopulation of study cohort described by Zierer et al. 2009[93]

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